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A CLINICOPATHOLOGICAL STUDY IN PATIENTS WITH URINARY BLADDER NEOPLASMS AMONG SUDANESE PATIENTS

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DEDICATION

To the soul of my teacher Dr. El Taib El Asha, the head of the Pathology Department, Faculty of Medicine, Omdurman Islamic University (1992-2002), who died of this tumour....

To my great parents, who kept encouraging me....

To my patient husband & lovely children who suffered a lot during the preparation of this study....

With love, faith & respect.

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List of abbreviations

CIS : Carcinoma in situ

ISUP : International Society of Urological Pathology

WHO : World Health Organization

BCG : Bacillus Calmette-Guerin

IARC : International Agency for Research on Cancer

FISH : Fluorescent in situ hybridization

TCC : Transitional cell carcinoma

EGFR : Epidermal growth factor receptor

RB1 : Retinoblastoma gene 1

BTA : Bladder tumour antigen

NMP22 : Nuclear matrix protein 22

TUBP : Transurothelial biopsy

TURBT : Transurethral resection of bladder tumour

PUNLMP: Papillary urothelial neoplasm of low malignant potential

SQCC : Squamous cell carcinoma

SCC : Small cell carcinoma

MFH : Malignant fibrous histocytoma

MALT : Mucous associated lymphoid tumours

UBN : Urinary bladder neoplasms

ABSTRACT

This is a retrospective study conducted on Sudanese patients in the period January 2004 to December 2005 at Ibn Sina Hospital, Soba University Hospital, as well as the National Health Laboratory, Khartoum, Sudan.

The study aimed to determine the histopathological pattern of urinary bladder neoplasms and to show the distribution of age, sex, original distribution, risk factors, and clinical presentations of it in Sudanese patients with verification of the different therapeutic options and the outcome.

One hundred and six patients with urinary bladder neoplasms were included in the study. The commonest age group was 60-<80 years and the age for all patients ranges between 18-90 years with a male to female ratio of 6.2:1.

Urinary bladder neoplasms showed some ethno-geographic variations in Sudan. The majority of these cases were from the Northern and Western regions and a high incidence was found among Gaaleen tribe. Transitional cell carcinoma was found in 67.9% of the patients, 44% of them were high grade and 36.8% were muscle invading at presentation. Both WHO (1973) and the WHO/ISUP

(2004) grading systems were used in this study and close findings were obtained. This study revealed a significant relationship between tumour grade as well as muscle invasion and the outcome of urinary bladder neoplasms (P=0.006 and P=0.002, respectively).

Squamous cell carcinoma accounts for 24.5% of the cases, 84.6% of them had a positive history of urinary shistosomiasis. In this study, there was a highly significant relationship between urinary shistosomiasis and squamous cell carcinoma (P=0.0001). Nevertheless, no correlation between tobacco smoking and transitional cell carcinoma was found (P=0.275). These findings compared with those from other countries.

In conclusion, urinary bladder neoplasms are increasing in number in Sudan and they share some epidemiological features with other developing countries and others with developed countries. Poor record keeping and registration may have contributed to the low number of patients enrolled into the study. There is a need for thorough prospective study to find out the actual prevalence and related risk factors of urinary bladder neoplasms in Sudan. We stress the significance of the public health education and the benefits of bladder cancer screening program to improve the outcome.

بسم الله الرحمن الرحيم

ملخص الاطروحة

هذه دراسة قهقرية أُجريت على المرضى السودانيين فى الفترة من يناير 2004 و حتى ديسمبر2005 فى كلٍّ من مستشفى ابن سينا و مستشفى سوبا الجامعى بالإضافة إلى المعمل الصحى القومى بالخرطوم – السودان.

تهدُف هذه الدراسة الى تحديد النمط النسيجى الإمراضى لأورام المثانة البولية الخبيثة وتوضيح توزيع كلٍّ من العمر ، الجنس، الأصل، عوامل الخطورة، والعلامات السريرية وكذلك التحقُّق من الخيارات العلاجية المختلفة وحصيلة المرض.

شملت الدراسة 106 مريضاً تراوحت أعمارهم ما بين 18-90 عاماً، وكانت المجموعة العمرية الأكثر شيوعا هى 60- وأقلّ من80 عاما. نسبة الذكور للإناث 6.2 :1 . كانت أكثر الحالات من شمال ثم غرب السودان وأكثر القبائل تأثراً كانت هى قبيلة الجعليين.

أوضحت الدراسة أنَّ النمط النسيجى الأكثر شيوعاً هو سرطانة الخلية العابرة (المتحولة) وُجدت فى (67.9 %) من المرضى، 44% منهم فى مرحلة مرضية عالية و 36.8% كانت غازية للعضلات عند قدومهم.

كلٍّ من نظام منظمة الصحة العالمية (1973) ونظام منظمة الصحة العالمية / الجمعية العالمية لاختصاصى علم أمراض المسالك البولية (2004) لدراسة مراحل المرض قد أُستعملا فى هذه الدراسة وقد تمَ الحصول على نتائج متقاربة.

هذه الدراسة أظهرت علاقة ذات مغزى بين مرحلة الورم المرضية وكذلك غزوه للعضلات وحصيلة أورام المثانة البولية الخبيثة (P= 0.002 و P=0.006 على التوالى).

سرطانة الخلية الظهارية شكّلت 24.5 % من الحالات. 84.6% من هؤلاء المرضى لهم تأريخ ايجابى للاصابة ببلهارسيا

المجارى البولية. فى هذه الدراسة هناك علاقة ذات مغزى عالى بين بلهارسيا المجارى البولية وسرطانة الخلية الظهارية (P =0.0001) ومع ذلك لم توجد علاقة ذات مغزى بين تدخين التبغ وسرطانة الخلية العابرة (P = 0.275). هذه النتائج تمّت مقارنتها مع نتائج دراسات مشابهة من دول اخرى.

ولقد خلُصت هذه الدراسة إلى أنَّ أعداد أورام المثانة البولية الخبيثة فى زيادة، و أنَّ السودان يشارك بعض الدول النامية الاخرى فى بعض الخصائص البيئية و يشارك الدول المتقدمة فى خصائص أخرى. سوء حفظ السجلات و التسجيل له ضِلع في قِلّة عدد المرضى الذين شملتهم الدراسة. هنالك حوجة لدراسة شاملة لمعرفة الانتشار الحقيقي و عوامل الخطورة المرتبطة بأورام المثانة البولية الخبيثة في السودان. و قد تطرَقت الدراسة لأهمية التثقيف الصِّحي و فوائد برامج الفحص الطبي الدوري لأورام المثانة البولية الخبيثة من أجل الوصول إلى نتائج أفضل.

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1-1 Introduction

Neoplasms of the bladder pose biologic and clinical challenges. Despite significant inroads into their origins and improved methods of diagnosis, they continue to exact a high toll in morbidity and mortality. Although there are improvements in detection and management of these neoplasms, the death toll remains at about 108, 310 annually worldwide.[1]

Carcinoma of the bladder is more common in men than in women, in industrialized than in developing nations, and in urban than in rural dwellers. About 80% of patients are between the ages of 50-80 years.[2]

About 95% of bladder tumours is of epithelial origin, the remainder being mesenchymal tumours. Most epithelial tumours are composed of urothelial (transitional) type cells, but squamous and glandular carcinomas also occur. Urothelial tumours represent about 90% of all bladder tumours.

There are two distinct precursor lesions to invasive urothelial carcinoma. The more common are the noninvasive papillary tumours which appear to arise from papillary urothelial hyperplasia.[3] The other precursor lesion is flat urothelial carcinoma, which is simply referred to as carcinoma in situ (CIS).

Many systems of grading urothelial neoplasms were proposed. A more recent classification, based on a consensus reached at a conference by the International Society of Urological Pathology (ISUP) in 1998, recognizes a rare benign papilloma, a group of papillary urothelial neoplasms of low malignant potential, and two grades of carcinoma (low and high grade). This system was adopted by the WHO in 2004. The staging system most commonly used is the TNM classification of bladder neoplasms.

A number of factors have been implicated in the causation of transitional cell carcinoma. Some of the more important contributors include; cigarette smoking, industrial exposure, *Shistosoma haematobium*, long-term use of analgesics and prior exposure of the bladder to radiation. How these influences induce cancer is unclear, but a number of genetic alterations have been observed in urothelial cell carcinoma.[4, 5]

Bladder tumours classically produce painless hematuria. Frequency, urgency, and dysuria occasionally accompany the hematuria.

Patients with urothelial tumours, whatever the grade, have a tendency to develop new tumours after excision, and recurrences may exhibit a higher grade. The risk of recurrence and progression is related to several factors, including tumour size, stage, grade,

multifocality, prior recurrence rate, and associated dysplasia and/or carcinoma in situ in the surrounding mucosa.[6-11]

Although cystoscopy and biopsy is the mainstay of diagnosis, carcinoma in situ that produces no or only subtle gross mucosal changes and early small papillary lesions may be difficult to detect. Of value in these circumstances are cytologic examinations and tests that detect the presence of various urine markers such as human complement factor H-related proteins, fibrin-fibrinogen degradation products, hyaluronidase, telomerase, mucins, nuclear matrix proteins, and DNA content.[12-15] The later diagnostic approach for DNA content is effective in differentiating high-grade tumours from the benign ones and detecting aneuploid high-grade lesions when there is uncertainty as to diagnosis.

The treatment for bladder cancer depends on the grade, the stage, and whether the lesion is flat or papillary. For small localized papillary tumours that are not high grade, the initial diagnostic transurethral resection is all that is done. When a patient presents with multifocal bladder tumours, instillation of topical chemotherapy into the bladder, in the immediate postoperative period, can reduce the likelihood of tumour recurrence. Topical immunotherapy consisting of intravesical instillation of an attenuated strain of *Mycobacterium tuberculosis* called Bacillus Calmette-Guerin

(BCG) is performed in patients who are at high risk of recurrence.[16] Radical cystectomy is performed in certain infiltrative tumours. Advanced bladder cancer is treated by chemotherapy.

Cancer of the bladder is known to remain localized for a relatively long time before it spreads extravesically. Nevertheless, it has always been looked at as a killing disease in Sudan.[17]

The main reason for this pessimistic outlook is the poor shape and advanced stage at which our patients present, making any effective surgical treatment difficult.

This study shows the pattern of urinary bladder neoplasms in Sudan as reviewed in two urological centers as well as the National Health Laboratory with regards to age, sex, origin, risk factors, clinical presentation and the histopathological classification, in addition to verification of different therapeutic options and outcome.

1-2 Literature Review

1-2-1 Normal Anatomy, Embryology and Histology:

The urinary bladder is a hollow, mostly muscular organ that stores urine until ready for release. It is located in the pelvis and related to the prostate and seminal vesicles in the male and vagina and uterus in the female. It is divided into the following portions: superior surface (also known as dome) and covered by the pelvic parietal peritoneum, posterior surface (also known as base), and the two inferolateral surfaces. The trigone is located at the base of the bladder and is continuous with the bladder neck, in which the posterior and inferolateral wall converge to open into the urethra. The lymphatic drainage of the bladder is primarily through the external and internal iliac nodes; portions of the bladder neck region may drain to the sacral or common iliac nodes.[18]

The bladder develops mainly from the vesical part of the urogenital sinus, but its trigone region is derived from the caudal ends of the mesonephric ducts.[19] The epithelium of the urinary bladder is entirely derived from endoderm of the urogenital sinus, whereas the lamina propria, muscularis propria, and adventitia develop from the surrounding splanchnic mesenchyme.[20]

The walls of the bladder are composed of three main layers; the mucosa, muscularis propria, and adventitia. The mucosa is formed by the epithelium, lamina propria, and (rarely) a continuous or discontinuous muscularis mucosa. The epithelium of the bladder has been traditionally referred to as transitional, but the term urothelium is more informative and accurate.[18] The urothelium of the contracted bladder is six to eight cells thick and those at the luminal surface are rounded or cupshaped. In the distended bladder the urothelium is much thinner and the cells are flattened.[21] The major function of the urothelium is to allow distention in the urinary organs during urine accumulation and contraction during the emptying of the urinary passages without breaking the cell contacts in the epithelium. In addition, it forms an important osmotic barrier between urine and the underlying tissue fluid.[22]

The urothelium has three layers: superficial, intermediate, and basal. The superficial layer is made up of single row of large, epitheloid cells having an abundant eosinophilic cytoplasm and referred to as umbrella cells. In electron microscopy, it has characteristic hexagonally arranged subunits. The intermediate cells have a cuboidal to low columnar shape, oval nuclei with finely stippled chromatin, moderately abundant cytoplasm, and well

defined margins. The basal layer is made up of cuboidal cells that lie on a thin continuous basal lamina.[18]

The lamina propria is composed of loose connective tissue containing a rich vascular network, lymph vessels, and a few elastic fibers. A rather prominent collection of arteries and veins is present in the midportion of the lamina propria and divides this layer into inner and outer zones. Smooth muscle cells are present in association with these vessels, usually as isolated bundles, sometimes as a discontinuous thin layer, and rarely as a continuous layer (muscularis mucosa).These muscle bundles should not be confused with those of muscularis propria when evaluating the depth of invasion of a bladder neoplasm. The muscularis propria is divided into inner and outer longitudinal layers and a central circular layer; these are best individualized in the bladder neck region.[18]

1-2-2 Epidemiology:

Bladder cancer is the seventh most common cancer world wide, with an estimated 260,000 new cases occurring each year in men and 76,000 in women.[23] It is the second most common urological cancer, [24] with the highest incidence rates of bladder cancer in Western Europe, North America and Australia. It

accounts for about 3.2 % of all cancers worldwide and is considerably more common in males than in females (ratio worldwide is about 3.2:1).[23]

The incidence of bladder epithelial tumours in the United States has been steadily increasing during the past years and is now more than 57,000 new cases annually.[25]

In the kingdom of Saudi Arabia (KSA) genito-urinary cancer (GUC) accounts for 9.2% of all cancer cases in KSA and the common GUC is bladder cancer.[26] Bladder cancer is the second most frequent cancer in Iraq in both sexes, [27] while urinary bladder malignant neoplasms account for only 8% of malignant neoplasms in Repuplic of Yemen.[28] In African countries, poor record keeping may have contributed to the low number of patients enrolled in some studies.[29]

In Sudan male patients predominate in all groups with a male to female ratio of 5:1 and the commonest age of presentation is 50 to 70 years old.[30] The incidence, morbidity, and mortality rates associated with bladder cancer vary by country, ethnicity, gender and age.[31] According to 1997 Surveillance , Epidemiology , and End Results data of the US National Cancer Institute, white persons had an incidence of 17.7 per 100,000 population while black persons had an incidence of 9.2 per 100,000 population .

Men have a risk that is at least three times greater than that of women. The age adjusted incidence for men was 28.2 per 100.000 populations, and it was 7.5 per 100,000 populations for women. Moreover, the life time risk of receiving a diagnosis of bladder cancer is 3.40% for men and 1.18% for women. Between 1998 and 1997, persons 65 years old had an incidence of 110.8 per 100.000 population while younger persons had an incidence of only 6.4 per 100.000 population .Statistically, the risk for 70 years old person is two to three times greater than that for a person 55 to 69 years old, and 15 to 20 times greater than for a person 30 to 54 years old.[31]

In terms of mortality, the World Health Organization estimated that 132,432 persons died of bladder cancer world wide in 2000.
In the United States approximately 12,200 individuals died of bladder cancer in 2000 .Men accounted for about two thirds of these deaths. The age adjusted mortality rate for bladder cancer was 3.2 per 100,000 in 1997. White persons had an age– adjusted mortality rate of 3.3 persons per 100,000 while Black persons had a mortality rate of 3.1 persons per 100,000. Although, Black persons have a much lower incidence of bladder cancer, they appear to have a mortality rate comparable to that of White persons. This finding suggests that black persons may receive a

diagnosis at a later stage of diseases, indicating a worse prognosis.[31]

1-2-3 Risk factors:

The risk factors for bladder cancer are both environmental and genetic.

1-2-3-1 Environmental risk factors:

Tobacco smoking:

Tobacco smoking is the major established and the number one environmental risk factor of bladder cancer. It is estimated that the risk of bladder cancer attributed to tobacco smoking is 66%for men and 30 % for women. The risk of bladder cancer in smokers is 2.6 fold that of non- smokers.[23]

The risk increases with increasing duration of smoking, and for those with the longest history of smoking (60 years or more) reaches approximately 6 times in men and 5 times in women[31]. The length of time that a person smokes appears to be the most important predictor of the risk. The aromatic amines contained in cigarette smoke are most likely responsible for this increased risk.[31]The excess of risk is observed also with increasing intensity of smoking (number of cigarettes per day) reaching maximum of about 3 for those smoking 40 or more cigarettes per day. The

increase of risk with the increasing duration and intensity of smoking is similar in both sexes. The risk of bladder cancer goes down after stopping smoking, and after 15 years cessation tends to be approximately that of non–smokers.[23]

The study of Zhang ZF, et al evaluated seventy three patients with bladder cancer for smoking history, occupational history, and chromosome 9 alterations. It supplies evidence suggestive of the link between smoking and chromosome 9 alterations in the etiology of bladder cancer and indicates that potential tumour suppressor genes on chromosome 9 may be involved in smoking-related bladder carcinogenesis.[32]

Occupational exposure:

Bladder cancer is associated with a number of occupations or occupational exposures. The first such association was observed in 1895 by Rehn who reported high rates of bladder cancer among men employed in the aniline dye industry.[23] Subsequent researches among dye workers identify the aromatic amines benzidene and 2-naphthylamine and possibly 1-naphthylamine, as bladder carcinogens. Work–related contact with chemicals, such as benzene derivatives and arylamines, likely account for 25% of all bladder cancer cases. Persons with professions involving heavy exposure to dyes, rubbers, textiles,

and chemicals demonstrate a high incidence of bladder cancer.[31] Recently, a population-based case-control study on hair dye use was conducted in 1514 cases of bladder cancer and an equal number of matched control subjects. After adjustment for cigarette smoking, women using permanent hair dyes at least once per month had 2.1 fold increased risk of bladder cancer compared with non users. Risk increased further to 3.3 fold for women using hair dyes for 15 years or longer.[31]

Huncharek M. and Kupelnick B. examined the methodology of observational studies that explored an association between personal use of hair dyes products and the risk of bladder cancer using a general variance-based meta-analytic method. The sensitivity performed, yielded statistically significant summery relative risk (RRs) ranging from 1.22 (1.11, 1.51) to 1.50 (1.30, 1.98), indicating that personal use of hair dye products increases bladder cancer risk by 22% to 50% vs. non-use.[33]

Phenacetin:

Several epidemiological studies indicate that chronic abuse of analgesics containing phenacetin greatly enhances the risk of developing urothelial cancer of the renal pelvis, ureter and bladder. The relative risk has been estimated in the range of 2.4 to more

than 6. Early cases have been reported from Scandinavia, Switzerland and Australia.[23]

Medicinal drugs:

The cytostatic agent, cyclophosphamide has long been associated with the development of leukemia and lymphoma. In addition, treatment with cyclophosphamide has been reported to be associated with an increased risk of squamous cell carcinomas and sarcomas, especially leiomyosarcomas. Similarly chlornphazine is associated with the development of bladder cancer.[23]

Chronic infections:

A potentially causative agent, particularly in Africa, is Schistosoma haematobium.This parasite is presumed to cause cancer by invoking chronic inflammation and interfering with the metabolism of cigarette smoke-related bladder mutagens. Interestingly most cancers caused by schistosomiasis are squamous cell in origin and appear in younger patients.[31]

Some authors suggested an association between bladder cancer and urinary tract infection and urinary tract stones. The underlying mechanism may lead to chronic irritation of the bladder epithelium, which may increase bladder cancer risk.[23]

Arsenic:

Arsenic is used in pesticides and some regions with high concentrations of arsenic in drinking water show a high rate of bladder caner. Several studies showed that use of drinking water containing chlorination byproducts or contaminated by arsenic might increase risk of bladder cancer.[23] Arsenic-contaminated water is a potential risk factor of bladder cancer (reported in Argentina, Chile, Bangladesh and Taiwan). An International Agency for Research of Cancer (IARC) Monographs Working Group reviewed in 2004 the relevant epidemiological studies and concluded that arsenic in drinking water is carcinogenic to humans (group 1) and that there is sufficient evidence that it cause urinary bladder cancer. Key evidence came from ecological studies in Chile and Taiwan (China) where large populations were exposed.[23]

Arsenic has been well documented as the major risk factor for black foot disease (BFD).[34] BFD is a unique peripheral vascular disease that was endemic in the South Western Coast of Taiwan, where residents had consumed high-arsenic artesian well water for more than 50 years. Long-term arsenic exposure has also been reported to be associated with bladder cancer mortality in a base-response relationship. Yang CY and et al implemented a tap water supply system in the early 1960s in the BFD endemic areas to

examine whether bladder cancer mortality decreases after the improvement of the drinking water supply system through elimination of arsenic exposure from artesian well water . Standardized mortality rations (SMRs) for bladder cancer were calculated for the BFD endemic areas for the years 1971 -2000. The study results showed that mortality from bladder cancer declined gradually after the improvement of the drinking water supply system to eliminate arsenic exposure from artesian well water. Based on the reversibility criterion, this finding strengthened the likelihood of the observed association between arsenic exposure and bladder cancer being causal.[34]

Researchers are studying other possible connections to bladder cancer including coffee, artificial sweeteners such as saccharine, diesel exhaust, pelvic radiation and others. Some connections can be made, but the evidence is not conclusive.

Environmental factors that may potentially reduce the risk of bladder cancer include the following: vitamin A; vitamin C; increased fluid intake and a low fat, high fruit and vegetable diet.[31]

1-2-3-2 Genetic factors:

Urothelial carcinoma is not considered a familial disease. However, several epidemiological studies showed that urothelial carcinomas have a familial component with a 1.5 to 2- fold

increased risk among first–degree relatives of patients.[23] The cytogenetic and molecular alterations are heterogeneous. Importantly, coamplification and simultaneous over expression of multiple adjacent oncogenes is often seen and it provides cells with significant growth advantages.[23]

Chromosomal abnormalities:

Invasively growing urothelial bladder cancer is characterized by presence of a high number of genetic alterations involving multiple different chromosomal regions. Particularly common (occurring in 30 % to 60% of tumors studied) are chromosome 9 monosomy or deletions of 9p and 9q as well as deletions of 17p, 13q, 11p, and 14q. The chromosome 9 deletions are the only genetic changes that are present frequently in superficial papillary tumours and occasionally in noninvasive flat tumours. [2]

Panani AD et al studied the nonracial aberrations of chromosomes 9 and 11 detected by FISH in 35 Greek patients with primary bladder tumours. They observed numerical aberrations of chromosomes 9 in 23 out of 27 tumours (85.18%). Monosomy 9 was detected in 12 cases (44.45%) and polysomy in 11 cases(40.74%).The statistical analysis of their study showed that polysomy 9 was linked to histological stage (P=0.024) and grade(P=0.01) of the tumours, while monosomy 9 was correlated

with tumour stage (P=0.050). Numerical aberrations of chromosome 11 were observed in 25 out of 35 cases (71.43%). Polysomy was detected in 24 cases (68.57%), while only one case (2.86%) had monosomy 11. Polysomy 11 were found mainly in high grade and advanced - stage tumours.[35]

Imad Fadl-Elmula, et al, explored the genetic alterations of 73 bladder Transitional Cell Carcinomas (TCCs), using G-banding, spectral karyotyping, and FISH analysis. They concluded that the karyotypic profile of bladder TCCs is characterized by non-random chromosomal aberrations varying from one or few changes in low grade and early stage tumours to massively rearranged karyotypes in muscle invasive ones. They observed that the karyotypic profile is dominated by losses of chromosomal materials. [36]

In another study, Fadl-Elmula, et al also found that rearrangements of chromosome 9 resulting in loss of material from 9p, 9q, or of the entire chromosome are the most frequent cytogenetic alterations. These observations are seen as the sole change as well as massively complex karyotypes, indicating that loss of Tumour Suppressor Genes (TSGs) from this chromosome is of major importance in urothelial carcinogenesis.[37]

Oncogenes:

Her2/neu is a transmembrane receptor tyrosine kinase without a known ligand. Its activation occurs through interaction with other members of the Epidermal Growth Factor Receptor (EGFR) gene family. HER2 is amplified in 10-20% and over expressed in10-50% of invasively growing bladder cancers. Amplifications or deletions of the adjacent topisomerase 2 alpha (TOP2A) are present in about 23% of HER2-amplified cases. TOP2A is the target of anthracyclines. Thus, the anatomy of the 17q23 amplicon may also influence the response to cytotoxic therapy regimens.[23]

H-ras is the only member of the ras gene family with known importance in urinary bladder cancer. H-ras mutations are almost always confined to specific alterations within the codons 12, 13 and 61. H-ras mutations have been reported in up to 45% of bladder cancers.[23]

The epidermal growth factor receptor (EGFR) is another member of the class II receptor family. (EGFR) is a transmembrane tyrosine kinase acting as a receptor for several ligands including epidermal growth factor (EGF) and transforming growth factor alpha. EGFR also severs as a therapeutic target for several drugs including small inhibitory molecules and antibodies.

EGFR is amplified in 3-5% and overexpresed in 30-50 of invasively growing bladder cancers.[23]

Cyclin- dependant kinases (CDKs) and their regulatory subunits are important promoters of the cell cycle. The cyclin D1 gene (CCND1) located at 11q13 is one of the most regionally amplified and over expressed oncogens in bladder cancer. About 10-20% of bladder cancers show gene amplification, and over expression has been reported in 30-50% of tumours.[23]

Tumors suppressor genes:

One of the genes that provide a growth advantage to affected cells in case of reduced expression or inactivation is the TP53 gene. It is located at 17q23 and encodes a 53KDa protein which plays a role in several cellular processes including cell cycle, response to DNA damage, cell death and revascularization. Mutations of the TP53 gene, mostly located in the central DNA binding position of the gene, are a hallmark of invasively growing bladder cancers.[23] An online query of the International Agency for Research on Cancer (IARC) data base (R7version, September 2002) at www.iarc fr/ p53 revaluated TP53 mutations in 40-60% of invasive bladder cancers.[38]

The retinoblastoma (RB1) gene product was the first tumor suppressor gene to be identified in human cancer. (RB1) which is

localized at 13q14 plays a crucial role in regulation of the cell cycle. Inactivation of (RB1) occurs in 30-80% of muscle invasive bladder cancers, most frequently as a consequence of heterozygous 13q deletions in combination with mutation of the remaining allele. A strong association has been found between (RB1) inactivation and muscle invasion.[23] Phenotypically different bladder tumours exhibit different patterns of cell cycle regulators and this may explain why these tumours have different propensity to progress to invasive tumours.[39]

1-2-4 Clinical course:

Hematuria or blood in urine is by far the most common symptom of bladder cancer. Eighty to ninety percent of patients have this finding, which may be gross or microscopic, on initial evaluation.[31] Salwa Sir Elkhatim found that the main presenting symptom was heamaturia occurring in 96% of Sudanese patients and it was described as total and painless in 82% of the cases.[30] Separately, individuals may note disturbances in their urinary habits. These include complaints of dysuria (painful urination), increased frequency, urgency of urination, or failed attempts to urinate. These symptoms are reported in about 20% of patients and could be indicative of early disease. Other findings, such as a

mass in the bladder or urethral obstruction are more suggestive of invasive disease. When the urethral orifice is involved, pyelonephritis may follow. Any systemic complaints point to extensive metastasis of the disease.[31]

Patients with urothelial tumors what ever the grade, have tendency to develop new tumors after excision, and recurrences may exhibit a higher grade. The risk of recurrences and progression is related to several factors including tumor size, stage, grade and multifocality, prior recurrence rate and associated dysplasia and/or carcinoma in situ in the surrounding mucosa. Recurrent tumors reflect new tumors in some cases, and in other instances they share the same clonal abnormalities as the initial tumor and represent a true recurrence of the initial as a result of shedding and implantation of the original tumor cells. [2]

The most important factors for progression-free survival are grade, presence of lamina propria, and associated carcinoma in situ. Papillomas, papillary urothelial cancer yield a 98% 10-year survival rate regardless of the number of recurrences; only a few patients (<10%) experience progression of their disease to higher–grade lesions. In contrast, only about 40% of individuals with a high grade cancer survive 10 years; the tumour is progressive in

65%. Aproximately 70% of patients with squamous cell carcinoma are dead within the year. [2]

The clinical challenge with these neoplsms is early detection and adequate follow up.

1-2-5 Diagnosis:

The clinical work up for potential bladder cancer should start with complete physical examination and history, with careful attention to the patient's smoking history, past history of schistosomiasis, use of phenacetin-containing analgesics and alkylating drugs and possible occupational exposures.

A urine analysis reveals heamaturia in the majority of cases. On occasion, it may be accompanied by pyuria. Azotemia may be present in a small number of cases associated with urethral obstruction. Anemia may be due to chronic blood loss which is usual or to replacement of the bone marrow with metastatic disease.

Exfoliated cells from normal and abnormal urothelium can readily be detected in voided urine specimens. Exfoliative cytology is of little practical value in the initial evaluation of most bladder tumors because of their accessibility to formal biopsy. However it is most useful in the following situations: detection of tumours

associated with extensive chronic inflammation in which the biopsy may be negative because of sampling, carcinoma in situ, and carcinomas hidden in bladder diverticulum. Specimens obtained from bladder irrigation are superior to those resulting from voided urine.[18]

The greatest value of urinary bladder cytology is in the follow-up evaluation of patients who have received surgical or radiotheraputic treatment for bladder carcinoma. In some cases the recurrence may not become clinically apparent until more than a year after the malignant cells have been detected in urine.

The most distinctive cytological features of transitional cell carcinoma, which can be useful for their recognition at a metastatic site, are the spindle, pyramidal, and racquet- like shape of the tumour cells, eccentric nuclei, and cytoplasmic evidence of both squamous and glandular differentiation (including endo-cytoplasmic interfaces and intra cytoplasmic vacuoles).[18]

Topical and systemic therapeutic agents and treatment modalities such as thiotepa and mitomycin C, cyclophosphamide, BCG, radiotherapy, photodynamic and laser treatment, and gene therapy produce a host of changes and alterations in the bladder, some of them mimicking cancer. Pathologists must be aware that,

following these types of treatment, the clinical usefulness of urinary cytology is reduced.[40]

Cytology is very sensitive in detecting higher-grade and stage cancers (82% to 90%), but is less sensitive in detecting superficial or well-differentiated lesions (50%), because the cells are very similar to those of normal bladder mucosa. Sensitivity of detection using exfoliated cells may be enhanced by flow cytometry.[24]

Although cystoscopy and biopsy are the mainstays of diagnosis, carcinoma insitu that produces no or only subtle gross mucosal changes and early small papillary lesions may be difficult to detect. Of value in these circumstances are cytological examination and tests that detect the presences of various urine markers such as human complement factor H-related proteins, telomerase, fibrin-fibrinogen degradation products, mucins, CEA, hyaluronic acid, hyaluronidase, nuclear matrix proteins, and DNA contents. The predominant limitation of many of the tests measuring urine markers is their relatively low specificity, because positive test results may occur in conditions associated with injured endothelium.[2]

Bladder cancers may be detected using intravenous urography, ultrasound computerized tomography, or magnetic resonance imaging where filling defects within the bladder are noted. However the presence of cancer is confirmed by cystoscopy and biopsy so imaging is useful primarily for evaluating the upper urinary tract and in staging the more advanced lesions.[24]

Flow cytometric and image analysis techniques have been developed for the evaluation of DNA abnormalities in cytological specimens from the bladder. These have reached a degree of accuracy equivalent to that of conventional cytological examination.[18] Bartoltti R et al compared the diagnostic accuracy of urinary cytology, urinary bladder cancer (UBC) markers, and bladder tumor antigen (BTA), and microsattelite sequence alterations in 42 patients. Urinary cytology confirmed the presence of TCC in 13 (3%) of the studied patients. The BTA-t markers allowed the identification of 73.3% of cases with 50.20% specificity. The UBC markers identified 63, 3% of cases with 41.6% specificity. Microsatellite analysis permitted the identification of 83.3% of the tumors with 100% specificity. DNA demonstrated high sensitivity in patients affected by superficial (81.4%) or grade 1 (80%) tumors.[41]

Grossman HB et al investigated whether a point-of-care proteomic test that measures the nuclear matrix protein NMP22 in voided urine could enhance detection of malignancy in patients with risk factor or symptoms of bladder cancer. On his study, the diagnosis of bladder cancer, based on cystoscopy with biopsy, was accepted as the reference standard. The performance of the NMP22 test was compared with voided urine cytology as an aid to cancer detection. Bladder cancer was diagnosed in 79 patients. The NMP22 assay was positive in 44 of 79 patients with cancer (sensitivity 55.7%; 95% confidence interval [CI], 44.1%-66.7%) whereas cytology test results were positive in 12 of 76 patients (sensitivity, 15.8%; 95%CI, 7.6%-24.0%).The specificity of the NMP22 assay was 85.7 %(95%CI, 83.8%-87.6%) compared with 99.2% for cytology. The proteomic marker detected 4 cancers that were not visualized during initial endoscopies, including 3 that were muscle invasive and 1 carcinoma in situ. It can be concluded that the non–invasive point-of-care assay for elevated urinary NMP22 protein can increase the accuracy of cytology, with test results available during the patient visit.[42]

Cystoscopy, a procedure in which a camera is inserted through the urethra with the patient under a local anesthetic, is performed after the IVP. Its purpose is to look for tumors and

irregularities in the bladder. The surgeon should record the number of tumors as well as their location, size, and shape. Any reddened or hardened areas that could be indicative of carcinoma in situ also should be noted. During cystoscopy, bladder wash can be performed to obtain cells for cytological evaluation.

Histologic examination of tissue, whether obtained by cystoscopically directed, random, or selected-site biopsies, is currently the primary means of detecting and monitoring bladder neoplasms. Depending on the amount of tissue available, histology can be used to gauge the extent of the process and evaluate its biological potential. The major limitation of histologic examination is inadequate sampling, although the inability to accurately determine the viability and future behavior of certain neoplastic lesions represent a further drawback. Even with adequate samples, accurate histologic evaluation may be impeded by suboptimal preparations. Details of cellular structure can be discerned in specimens fixed in phosphate-buffered formalin but are more easily appreciated in tissues fixed in zinc formalin or picric acid-based solutions such as Bouins´s or Hollande´s.[43]

Immunohistochemichally, transitional cell carcinomas, the commonest bladder cancer, express various keratin types. A difference in pattern has been noted among basal cells, transitional

cells and umbrella cells (when present).[44]There is consistent expression of CK20, in stark contrast with the morphologically similar transitional cell carcinoma of the ovary.[45] The CK20 positivity is particularly common and strong in the high grade-tumours.[46]The coordinate expression of CK7 and CK20 is a particularly reproducible feature of transitional cell carcinoma,[47] and is usually maintained in the metastatic foci.[48] An increased expression of CK8 and CK18 has been found at the interface between tumor and stroma.[49] In general, the expression of CK18 is decreased in higher–grade and higher stage tumors but many exceptions occur.[49]Two relatively new useful markers for transitional cell carcinoma are thrombomodulin and uroplakin III. The former is very sensitive but not very specific (in that it also stains most squamous cell carcinomas and mesotheliomas), whereas the latter has a high degree of specificity but is only moderately sensitive.[51, 52, 53] Other markers commonly expressed by these tumours are CEA and Cathepsin B (particularly in high grade lesions), [54, 55, 56] CA19-9, [57] CD15 (Leu-M1),[58] survivin,[59] and androgen reseptors.[60]

Some tumors are also immunoreactive for Human Chorionic Gonadotrophin (HCG), Human Placental Lactogen, and SP-1, especially in the most pleomorphic areas[60, 61]; this can occur in the

absence of morphologic evidence of trophoblastic differentiation by the tumour.

Deletion of ABO blood group antigens is a common finding in transitional cell carcinoma, particularly in those having high grade microscopic features. This alteration can only be evaluated in “secretor” individuals, whose urothelium normally express these markers. A related abnormality is the expression of Lewis X antigen (which is absent in normal urothelium) in over 85% of transitional cell carcinoma regardless of tumor stage and grade.[62] Interestingly the loss of blood group antigens is often associated with an over expression of the epidermal growth factor receptor.[63]

The lack of ABO antigen expression in certain bladder tumours is due to the allelic loss of the ABO glycosyltransferase-encoding genes and in some of these tumours the loss involves the surrounding chromosomal region at 9q34.1-4.[64]

The immunohistochemical expression of the extracelluler matrix (ECM) components tenascin, fibronctin, collagen type IV and laminin is measured by different studies and correlated with clinicopthological features to clarify the prognostic value of these molecules and their role in tumour progression. Ioachim E, et al, studied 103 tumour specimens, obtained during transurethral resection of bladder tumour (TURBT), immunohistochemically and

concluded that levels of tenascin might be valuable for predicting the risk of early recurrence. The expression of tenascin, fibronectin and collagen type IV seems to be correlated with more aggressive tumour behavior. Furthermore, their interrelationship could indicate that they are involved in remodeling of bladder cancer tissue probably influencing tumour progression.[64]

The expression of angiopoietin-1 and -2 which are antagonistic angiogenic factors that regulate tumor growth were assessed immunohistochlemically by Oka N, et al in tissue sections from 52 transitional cell carcinomas of the bladder. Normal bladder specimens were also resected during each operation as controls. The expression angiopoietins were related to the clinico- pathological variables of the tumors. Positive immunostaining was detected in 18 samples (35%) for angiopoietin-1 and in 23 (44%) for angiopoietin-2. There was no significant difference in survival according to tumor angiopoietin-1status in the patients, but in contrast the overall survival of patients with angiopoietin-2 positive tumor was significantly lower than those with angiopoietin-2 negative tumors($P<0.05$). Positive angiopoietin-2 expression was significantly correlated with histological grade ($P=0.026$), histological stage ($P=0.009$) and poor prognosis ($P<0.05$).On multivariate analysis, positive angiopoitin-2

expression was an independent negative predictor for survival (P=0.042).These results suggests that angiopoietin-2 over expression is associated with tumour progression, thereby indicating a poor prognosis for some patients treated by surgical resection for bladder carcinoma.[66]

Ultrastructurally, high grade transitional cell carcinomas are accompanied by a decrease of specialized junctions. Pleomorphic microvilli are apparent by scanning electron microscopy regardless of tumour grade.[18]

1-2-6 Classification of urinary bladder tumours:

About 95% of bladder tumors are of epithelial origin, the remainders being mesenchymal tumours [*](WHO histological classification of tumours of the urinary tract). Most epithelial tumours are composed of urothelial (transitional) type cells and are thus interchangeably called urothelial or transitional tumours. [2]

*WHO histological classification of tumours of the urinary tract

Urothelial tumours
Infiltrating urothelial carcinoma
  with squamous differentiation
  with glandular differentiation
  with trophoblastic differentiation
  Nested
  Microcystic
  Micropapillary
  Lymphoepithelioma-like
  Lymphoma-like
  Plasmacytoid
  Sarcomatoid
  Giant cell
  Undifferentiated
Non-invasive urothelial neoplasia
  Urothelial carcinoma in situ
  Non-invasive papillary urothelial carcinoma, high grade
  Non-invasive papillary urothelial carcinoma, low grade
  Non-invasive papillary urothelial neoplasia of low malignant Potential
  Urothelial papilloma
  Inverted urothelial papilloma

Squamous neoplasms
Squmous cell carcinoma
Verrucous carcinoma
Squamous cell papilloma

Glandular neoplasms
Adenocarcinoma
  Enteric
  Mucinous
  Signet ring cell
  Clear cell
Villous adenoma

Neuroendocrine tumours
Small cell carcinoma
Carcinoid
Paragangilioma

Melanocytic tumours
Malignant melanoma
Nevus

Mesenchymal tumours
Rhabdomyosarcoma
Leiomyosarcoma
Angiosarcoma
Osteosarcoma
Malignant fibrous histocytoma
Leiomyoma
Haemangioma
Others

Haematopoitic and lymphoid tumours
Lymphoma
Plasmacytoma

Miscellaneous tumours
Carcinoma of skene, Cowper and Little glands
Metastatic tumours and tumours extending from other organs

1-2-6-1 Urothelial (Transitional) cell tumours:

These represent about 90% of all bladder tumors. They run the gamut from small benign lesions that might never recur to aggressive cancers associated with high risk of death. Many of these tumors are multifocal at presentation. Although most commonly seen in the bladder any of the lesions may be seen at any site where there is urothelium; from the renal pelvis to the distal urethra. [2]

Morphologic features:

Urothelial tumors can arise anywhere in the bladder. In a series of about 1000 cases, the location was listed as follows: lateral walls, 37%; posterior wall, 18%; trigone,12%; neck 11%; ureteric orifices, 10%; dome,8%; and anterior wall,4%. They have also been reported within diverticula.[67]

The pattern of growth may be exophytic or endophytic, or a combination of both. When exophytic, the tumour may adopt a papillary configuration (with central fibrovascular cores) or a solid (nodular) appearance. When growing endophytically (especially if well-differentiated), it may result in nested formations in the lamina propria, which may be under diagnosed as von Brunn's nests cystitis glandularis/cystica. Stromal invasion by the tumour proceeds in two stages: invasion of the lamina propria and

invasion of the muscle layer. Detection of the former is a difficult somewhat subjective and relatively unimportant exercise. Conversely, detection of muscle invasion is of great consequence because of its influence on therapy and prognosis.[18]

There are two distinct precursor lesions to invasive urothelial carcinoma. The more common are non-invasive papillary tumours, which appear to arise from urothelial dysplasia.[3] Urothelial dysplasia has appreciable loss of polarity with nuclear rounding and crowding and cytologic atypia that is not severe enough to merit a diagnosis of carcinoma in situ. The other precursor lesion is flat urothelial carcinoma, which is simply referred to as carcinoma in situ (CIS).[2]

Grading of urothelial tumours:

Several classification systems of bladder transitional cell carcinoma have been proposed over the years. These represent attempts at grading the increasing degrees of architectural and particularly cytological disarrays of a single tumor type.

The first widely used grading system for these tumours was that proposed by Ash in 1940. He thought that even the better differentiated papillary tumors should be classified as carcinoma because of their tendency to recur locally and also because the microscopic pattern does not always conform to the clinical

behavior, a fact that recent series have confirmed. The alternative terminology proposed by Mostofi in 1960 and adopted by the American Bladder Tumour Registry and the WHO in 1973, grades tumours into a rare totally benign papilloma and three grades of transitional cell carcinoma (grade I, II, and III). A more recent classification, based on a consensus reached at a conference by the International Society of Urological pathology (ISUP) in 1998, recognizes a rare benign papilloma, a group of papillary urothelial neoplasms of low malignant potential, and two grades of carcinoma (low and high grade). Its main features are the division of the neoplastic lesions into flat and papillary and the separate evaluation of the papillary neoplasms for grade (based on architecture and cytology) and invasiveness (divided into lamina propria and muscularis propria levels).[18]

The presently recommended nomenclature by the WHO is similar to the WHO/ISUP classification of 1998, but the diagnostic criteria are further defined for practice. The terms non-invasive have been added to low and high grade papillary carcinoma to emphasize biologic differences between these tumours and infiltrating urothelial cancer.[23]

Non-invasive urothelial tumours:

Urothelial papilloma:

Exophytic urothelial papilloma is composed of a delicate fibrovascular core covered by urothelium indistinguishable from that of the normal urothelium. It represents 1-4% of bladder tumours, most commonly seen in younger patients. The tumour usually arises singly as small (0.5-2.0 cm), delicate structures, superficially attached to the mucosa by a stalk. Urothelial papillomas rarely recur. Histologically, the lesion is characterized by discrete papillary fronds, with occasional branching in some cases, but without fusion. The stroma may show edema and or scattered inflammatory cells, the epithelium lacks atypia and the superficial cells (umbrella cells) are often prominent. Mitoses are absent to rare and, if present are basal in location and not abnormal. The lesions are diploid, mitoses rare and proliferation rates low as deemed by immunohistochemical assessment of e.g. Ki-67 expression. Cytokeratin 20 expression is identical to that in normal urothelium i.e. in the superficial (umbrella) cells only.[23]

Inverted papilloma is a benign urothelial tumour that has an inverted growth pattern with normal to minimal cytologic atypia of the neoplastic cells. Histologically, anastamosing islands and cords

of uniform width and distribution appear as if a papillary lesion had invaginated into the lamina propria.[23]

Papillary urothelial neoplasm of low malignant potential (PUNLMP):

This is a papillary urothelial tumour which resembles the exophytic urothelial papilloma, but shows increased cellular proliferation exceeding the thickness of normal urothelium. The incidence is three cases per 100.000 individuals per year. Histologically, the papillae are discrete, slender and none fused and are lined by multilayered urothelium with minimal to absent cytologic atypia. The cell density appears to be increased compared to normal. The polarity is preserved and there is an impression of predominant order with absent to minimal variation in architectural and nuclear features. The nuclei are slightly enlarged compared to normal. The basal layers show palisading and the umbrella cell layer is often preserved. Mitoses are rare and have a basal location. The tumours are predominantly diploid. PUNLMP may recur with the same morphology, are not associated with invasion, and only rarely recur as higher-grade tumours associated with invasion and progression.

Non-invasive papillary urothelial carcinoma, low grade:

Is a neoplasm of urothelium lining papillary fronds which show an orderly appearance, but easily recognizable variations in architecture and cytologic features. The incidence is five cases per 100,000 individuals per year. Histologically, the tumour is characterized by slender, papillary stalks which show frequent branching and minimal fusion. It shows an orderly appearance with easily recognizable variations in architectural and cytologic features even at scanning power. In contrast to PUNLMP, it is easy to recognize variations in nuclear polarity, size, shape, and chromatin pattern. The nuclei are uniformly enlarged with mild differences in shape, contour and chromatin distribution. Nucleoli may be present but inconspicuous. Mitoses are infrequent and may occur at any level but are more frequent basally. Expression of cytokeratin 20, CD44, p53 and p63 immunostaining is intermediate between that of PUNLMP and non-invasive high grade papillary urothelial carcinoma. The tumours are usually diploid. Recurrence is common and occurs in 48-71% of the patients. Progression to invasion and cancer death occurs in less than 5% of cases.[23]

Non-invasive papillary urothelial carcinoma, high grade:

Is a neoplasm of urothelium lining papillary fronds which show a predominant pattern of disorder with moderate-to-marked architectural and cytologic atypia. Histlogically, the tumour is characterized by a papillary architecture in which the papillae are frequently fused and branching, although some may be delicate. It shows a predominant pattern of disorder with easily recognizable variations in architectural and cytologic features even at scanning power. In contrast to non-invasive low grade papillary urothelial carcinoma, it is easy to recognize more marked variations in nuclear polarity, size, shape, and chromatin pattern. The nuclei often show pleomorphism with moderate–to-marked variation in size and irregular chromatin distribution. Nucleoli are prominent. Mitoses are frequent, may be atypical, and occur at any level, including the surface. The thickness of the urothelium may vary considerably and often with cell dyscohesion. Detection of cytokeratin 20, p53, and p63 is more frequent than in low grade tumours. The tumours are usually aneuploid.[23]

Urothelial carcinoma in situ (CIS):

Urothelial carcinoma in situ is defined as a non-papillary, i.e. flat lesion in which the surface epithelium contains cells that are cytologically malignant.[23] This lesion is by definition high grade and

hence not assigned a grade.[2] De novo (primary) carcinoma in situ accounts for less than 1-3% of urothelial neoplasms, but is seen in 45-65% of invasive urothelial carcinoma. It is present in 7-15% of papillary neoplasms.[68] Macroscopically, the mucosa may be unremarkable or erythematous and edematous. Mucosal erosion may be present. Histologically, urothelial carcinoma in situ shows nuclear anaplasia identical to high grade urothelial carcinoma. The enlarged nuclei are frequently pleomorphic, hyperchromatic, and have a coarse or condensed chromatin distribution; they may show large nucleoli. Mitoses including atypical ones are common and can extend to the upper cell layers. The cytoplasm is often eosinophilic or amphophilic. There is loss of cell polarity with irregular nuclear crowding.[69, 70]The neoplastic change may or may not involve the entire thickness of the epithelial layer and umbrella cells may be present. It may be seen at the basal layer only or may overly benign appearing epithelium. Individual cells or clones of neoplastic cells may be seen scattered amidst apparently normal urothelial cells and this is referred to as pagetoid spread.[71]

Infiltrating urothelial carcinoma:

Infiltrating urothelial carcinoma is defined as a urothelial tumour that invades beyond the basement membrane. The histology of infiltrating urothelial carcinoma is variable. These carcinomas are

graded as low grade and high grade depending upon the degree of nuclear anaplasia and some architectural abnormalities. Some cases may show relatively bland cytology.

The most important element in pathologic evaluation of urothelial cancer is recognition of the presence and extent of invasion. In early invasive urothelial carcinomas, foci of invasion are characterized by nests of, clusters, or single cells within the papillary cores and/or lamina propria. It is recommended that the extent of lamina propria invasion in pT1 tumor should be stated. The depth of lamina propria invasion is regarded as a prognostic parameter in pT1 cancer. Morphologic criteria useful in assessing of lamina propria invasion include the presence of desmoplastic stromal response, tumor cells within the retraction space, and paradoxical differentiation (invasive nests of cells with abundant eosinophilic cytoplasm at the advancing edge of infiltration). Recognition of invasion may be problematic because of tangential sectioning, thermal and mechanical injury, marked inflammatory infiltrates obscuring neoplastic cells and inverted or broad front growth.[23]

The histology of infiltrative urothelial carcinoma has no specific features and shows infiltrating cohesive nests of cells with moderate to abundant amphophilic cytoplasm and large

hyperchromatic nuclei. In larger nests, palisading of nuclei may be seen at the edges of the nests. The nucleus is typically pleomorphic and often has irregular contours with angular profiles. Nuclei are highly variable in number and appearance with some cells containing single or multiple nucleoli and others having large eosinophilic nucleoli. Foci of marked pleomorphism may be seen, with bizarre and multinuclear tumor cells. Mitotic figures are common, with numerous abnormal forms. The invasive nests usually induce a desmoplastic stromal reaction which is occasionally pronounced and may mimic a malignant spindle cell component, a feature known as pseudosarcomatous stromal reaction.[23]

Histologic variants:

Urothelial carcinoma has a propensity for divergent differentiation with the most common being squamous followed by glandular. Virtually the whole spectrum of bladder cancer variants may be seen in variable proportions accompanying otherwise typical urothelial carcinoma. Divergent differentiation frequently parallels high grade and high stage urothelial cancer. When small cell differentiation is present, even focally, it portends a poor prognosis and has different therapeutic ramifications, and hence should be diagnosed as small cell carcinoma.[23]

Infiltrating urothelial carcinoma with squamous differentiation:

Squamous differentiation, defined by the presence of intercellular bridges or keratinization, occurs in 21% of urothelial carcinoma of the bladder. Its frequency increases with grade and stage. Detailed histologic maps of urothelial carcinoma with squamous differentiation have shown that the proportion of the squamous component may vary considerably, with some cases having urothelial carcinoma in situ as the only urothelial component. The diagnosis of squamous cell carcinoma is reserved for pure lesions without any associated urothelial component, including urothelial carcinoma in situ. Tumours with any identifiable urothelial element should be classified as urothelial carcinoma with squamous differentiation and an estimate of the percentage of squamous component should be provided. Squamous differentiation may show basaloid or clear cell features. Cytokeratin 14 and L1 antigen have been reported as immunohistochemical markers of squamous differentiation. Uroplakins are expressed in urothelial carcinoma and not in squamous differentiation.[23]

The clinical significance of squamous differentiation remains uncertain, but seems to be an unfavorable prognostic feature in such patients undergoing radical cystectomy, possibly, because of

its association with high grade tumors. Squamous differentiation was predictive of a poor response to radiation therapy and possibly also to systemic chemotherapy.[23]

Infiltrating urothelial carcinoma with glandular differentiation:

Glandular differentiation is less common than squamous differentiation and may be present in about 6% of ureothelial carcinomas of the bladder. Glandular differentiation is defined as the presence of true glandular spaces within the tumour. These may be tubular or enteric glands with mucin secretion. A colloid mucinous pattern characterized by nests of cells floating in extracellular mucin occasionally with signet ring cells may be present. Pseudoglandular spaces caused by necrosis or artifact should not be considered evidence of glandular differentiation. Cytoplasmic mucin containing cells are present in 14-63% of typical urothelial carcinoma and not considered to represent glandular differentiation. The diagnosis of adenocarcinoma is reserved for pure tumors. A tumour with mixed glandular and urothelial differentiation is classified as urothelial carcinoma with glandular differentiation and an estimate of the percentage of glandular component should be provided. The expression of MUC5AC-apomucin may be useful as immunohistochemichal marker of glandular differentiation in urothelial tumours. The

clinical significance of glandular differentiation and mucin positivity in urothelial carcinoma remains uncertain.

Nested variant:

The nested variant of urothelial carcinoma is an aggressive neoplasm with less than 50 reported cases.[23] There is marked male predominance, and 70% of patients died 4-40 months after diagnosis, in spite of therapy. This rare pattern of urothelial carcinoma was first described as a tumor with a deceptively benign appearance that closely resembles von Brunn nests infiltrating the lamina propria. Some nests have small tubular lumens. Nuclei generally show little or no atypia, but invariably the tumor contains foci of unequivocal anaplastic cells exhibiting enlarged nuclei and course nuclear chromatin. This feature is most apparent in deeper aspects of the tumour. Useful features in recognizing this lesion as malignant are the tendency for increasing cellular anaplasia in the deeper aspects of the lesion, its infiltrative nature, and the frequent prescience of muscle invasion.[23] Moreover, immunohistochemical studies showed nested variant of urothelial carcinoma to have higher MIB-1expression than florid von Brunn nests (8.8% vs. 2.8%, P=0.01).[72]

Microcystic variant:

Occasionally urothelial carcinoma shows a striking cystic pattern with cysts ranging from microscopic up to 1-2 mm in diameter. The cysts are round to oval, sometimes elongated and may contain necrotic material or pail pink secretions. The cyst lining may be absent, flattened or urothelial and may show differentiation towards mucinous cells.[23]

Micropapillary variant:

Micropapillary bladder carcinoma is a distinct variant of urothelial carcinoma that resembles papillary serous carcinoma of the ovary, and approximately 60 cases were reported in the literature. There is a male predominance and patients age range from fifth to ninth decades with a mean age of 66 years. Histologically, micropapillary growth pattern is almost always associated with conventional urothelial carcinoma or rarely with adenocarcinoma.The micropapillary pattern exhibits two distinct morphologic features. Slender delicate fine papillary and filiform processes, often with a central vascular core, are observed on the surface of the tumours. On cross section they exhibit a glomeruloid appearance. In contrast, the invasive portion is characterized by tiny nests of cells or slender papillae, which are contained within tissue retraction spaces that simulate lymphatic

spaces. However, in most cases vascular/lymphatic invasion is present. The individual cells of micropapillary carcinoma show nuclei with prominent nucleoli and irregular distribution of the chromatin. Also, the cytoplasm is abundant, eosinophilic or clear, and mitotic figures range from few to numerous.

Immunohistochemical studies in one large series disclosed immunoreactivity of the micropapillary carcinoma in 20 of 20 cases for EMA, cytokeratin (CK) 7, CK 20, and Leu M 1. CEA was positive in 13 of 20 cases. Micropapillary carcinoma is a high grade, high stage variant of urothelial cancer with high incidence of metastases and morbidity.[23]

Carcinomas with a micropapillary component are morphologically identical in breast, urinary bladder and lung. Immunohistochemical stains are useful in distinguishing these lesions in that thyroid transcription factor-1 positivity suggests a lung primary, CK7 and estrogen receptor suggest a breast primary, and both CK7 and CK20 positivity suggest a urinary bladder primary.[73]

Lymphoepithelioma-like carcinoma:

Carcinoma that histologically resembles lymphepithelioma of the nasopharynx has recently been described in the urinary bladder, with fewer than 40 cases reported.[74] These tumours are

more common in men than in women (10:3, ratio) and occur in late adulthood (range 52-81 years, mean 69 years).The etiopathogenesis of this tumor is unknown, although it is suspected that it originate from modified urothelial cells, that are possibly derived from basal (stem) cells. Hybridization with Epstein-Barr virus encoded RNA has been reported to be consistently negative in different series. The tumor is solitary and usually involves the dome, posterior wall, or trigone.

Lymphepithelioma-like carcinoma may be pure, predominant or focally admixed with typical urothelial carcinoma, or in some cases with squamous cell carcinoma or adenocarcinoma.[43] Histologically, the tumor is composed of nests, sheets, and cords of undifferentiated cells with large pleomorphic nuclei and prominent nucleoli. The cytoplasmic borders are poorly defined imparting a syncytial appearance. The background consists of a prominent lymphoid stroma that includes T and B lymphocytes, plasma cells, histocytes, and occasional neutrophils or eosinophils, the later being prominent in rare cases. The epithelial cells of this tumor stain with several cytokeratin (CK) markers as follows: AE1/AE3, CK8, CK7, and they are rarely positive for CK20.[74] Differentiation from lymphoma may be difficult, but the presence of a syncytial pattern of large malignant cells with a dense

polymorphous lymphoid background is an important clue. Most reported cases of the urinary bladder had a relatively favorable prognosis when pure or predominant, but when lymphepithelioma-like carcinoma is focally present in an otherwise typical urothelial carcinoma, these patients behave like patients with conventional urothelial carcinoma alone of the same grade and stage.[74] This tumor, thus far has been found to be responsive to chemotherapy when it is encountered in its pure form.

Lymphoma-like and plasmacytoid variants:

The lymphoma-like and plasmacytoid variants of urothelial carcinoma are those in which the malignant cells resemble those of malignant lymphoma or plasmacytoma. Less than 10 cases have been reported. The histologic features of the lymphoma-like and plasmacytoid variants of urothelial carcinoma are characterized by the presence of single malignant cells in a loose or myxoid stroma.The tumour cells have clear or eosinophilic cytoplasm and eccentrically placed, enlarged hyperchromatic nuclei. Almost all of the reported cases have had a component of high grade urothelial carcinoma in addition to the single malignant cells. The tumour cells stain with cytokeratin (CK) cocktail, CK7and CK 20. Immunohistochemical stains for lymphoid markers have consistently been reported as negative.[23]

Sarcomatoid variant:

The term sarcomatoid variant of urothelial carcinoma should be used for all biphasic malignant neoplasms exhibiting morphologic and/or immunohistochemical differentiation. Microscopically, sarcomatoid carcinoma is composed of urothelial, glandular or small cell component showing variable degrees of differentiation. The mesenchymal component most frequently observed is an undifferentiated high grade spindle cell neoplasm. By immunohistochemistry, epithelial elements react with cytokeratins, whereas stromal elements react with vimentin or specific markers corresponding to mesenchymal differentiation. The sarcomatoid phenotype retains the epithelial nature of the cells by immunohistochemistry or electron microscopy. Recent molecular studies, strongly argue for a monoclonal origin of both components. Nodal and distant metastases at diagnosis are common and 70% of patients died of cancer at 1 to 48 months (mean 17 months).[75]

Urothelial carcinoma with giant cells:

High grade urothelial carcinoma may contain epithelial tumour giant cells or the tumor may appear undifferentiated resembling giant cell carcinoma of the lung. This variant is very infrequent.[23]

Urothelial carcinoma with trophoblastic differentiation:

Trophoblastic differentiation in urothelial carcinoma occurs at different levels. High grade invasive urothelial carcinomas may express ectopic human chorionic gonadotrophin (HCG) and other placental gonadotrophins at the immunohistochemical level only or may contain numerous syncytotrophoblastic giant cells.[23]

Clear cell variant:

The clear cell variant of urothelial carcinoma is defined by a clear cell pattern with glycogen-rich cytoplasm. The clear cell patter may be focal or extensive and awareness of this pattern is important in differential diagnosis with clear cell adenocarcinoma of the urinary bladder and metastatic carcinoma from the kidney and prostate.[76]

Lipid cell variant:

Very infrequently urothelial carcinomas contain abundant lipid in which lipid distended cells mimic signet ring cell adenocarcinoma.

Undifferentiated carcinoma:

This category contains tumours that can not be otherwise classified. They are extremely rare.

1-2-6-2 Squamous cell carcinoma:

This is defined as a malignant neoplasm derived from the urothelium showing histologically pure squamous phenotype.

Squamous cell carcinoma (SQCC) of the bladder is much less frequent than urothelial carcinoma. Worldwide, it constitutes about 1.3% of bladder tumours in males, and 3.4% in females. SQCC accounts for approximately 5% of bladder carcinomas in areas where schistosomiasis is not endemic, although in some series higher figures in the range of 10-15% have been obtained. However, SQCCs comprise approximately 75% of bladder tumours where schistosomiasis is endemic. The male: female ratio is lower than it is in cases of transional cell carcinoma but the age distribution is similar.[77] In the United States, the differences in histology by race are small, with, Whites having 95% urothelial and 1.3% squamous cell carcinomas (SQCCs), while the proportions are 87.8% and 3.2%, respectively, in Blacks.[23] In Africa, the majority of bladder cancers in Algeria and Tunisia (high incidence countries) are urothelial carcinomas, with SQCCs comprising less than 5%. In some West African countries (Mali, Niger), and in east and south-east Africa (Zimbabwe, Malawi, Tanzania), SQCC predominates, as it does in Egypt. In South Africa, there are marked differences in histology between Blacks (36% SQCC, 41%

urothelial) and Whites (2% SQCC, 94% urothelial). These observations (as well as clinical features such as sex ratio, mean age at diagnosis and stage) relate to the prevalence of infection with *Schistosoma haematobium*.[23]

Schistosomiasis and SQCC:

The evidence linking infection with *Schistosoma haematobium* with bladder cancer has been extensively reviewed. There are essentially three lines of evidence:

The first one is the clinical observations that the two diseases appear to frequently co-exist in the same individual, and that the bladder cancers tend to be of squamous cell origin rather than urothelial carcinomas. Secondly, many descriptive studies show a correlation between the two diseases in different populations. Thirdly, the different case-control studies, comparing infection with *S. haematobium* in bladder cancer cases and control subjects. Several studies investigated this relationship, taking as a measure of infection the presence of *Schistosoma haematobium* eggs in a urine sample, presence of calcified eggs identified in X-ray or information from a questionnaire. The estimated relative risk varied from 2 to 15 compared with non-infected subjects.[23]

Numerous explanations have been offered for the proposed association between schistosomiasis and human cancer:

Chronic infection and inflammation with increased cell turnover provide opportunities for mutagenic events, genotoxic effects and activation of carcinogens through several mechanisms, including the production of nitric oxide by inflammatory cells (activated macrophages and neutrophils). Altered metabolism of mutagens may be responsible for genotoxic effects. Quantitatively altered tryptophan metabolism in Schistosoma haematobium-infected patients result in higher consentrations of certain metabolites (e.g. indicant, anthranilic acid glucuronide, 3-hydroxyanthranilic acid, L-kynurenin, and others) in pooled urine. Some of these metabolites have been reported to be carcinogenic to the urinary bladder. Immunological changes have been suggested as playing a role.

Furthermore, secondary bacterial infection of schistosoma-infected bladders is a well documented event, and may play an intermediary role in the geneses of squamous cell carcinoma via a variety of metabolic effects. Nitrate, nitrite and N-nitroso compounds are detected in the urine of *S.haematobium*-infected patients. Nitrosamines are formed by nitrosation of secondary amines with nitrites by bacterial catalysis (or via urinary phenol catalysis); they may be carcinogenic to bladder mucosa. In addition, elevated levels of β-glucuronidase levels in schistosme-

infected subjects could increase the release of carcinogenic metabolites from their glucuronides.[23]

Genetic damage in the form of slightly increased sister chromatid exchange and micronucleus frequencies were seen in peripheral blood lymphocytes harvested from schistosomiasis patients, and micronuclei were more frequent in urothelial cells from chronic schistosomiasis patients than in controls.

Lundgren R, et al investigated SQCC cytogenetically by means of chromosome banding and they found a complex karyotype with many structural and numerical changes, including -9 and del (11p), aberrations that also have been noted in transitional cell carcinoma.[78]

Macroscopically, most squamous cell carcinomas are bulky, polypoid, solid, necrotic masses, often filling the bladder lumen.

Histologically, the diagnosis of squamous cell carcinoma is restricted to pure tumours.[79] The presence of keratinizing squamous metaplasia in the adjacent flat epithelium, especially if associated with dysplasia, supports a diagnosis of squamous cell carcinoma.

The invasive tumours may be well differentiated with well defined islands of squamous cells with keratinization, prominent intercellular bridges, and minimal nuclear pleomorphism. They may

also be poorly differentiated, with marked nuclear pleomorphism and only focal evidence of squamous differentiation.[23] A basaloid pattern has been reported.[80]

Prognostic and predictive factors:

Patient related factors, e.g. sex and age are not prognostic in squamous cell bladder cancer. In contrast, T-stage, lymph node involvement and tumour grade have been shown to be of independent prognostic value. Patients undergoing radical surgery appear to have an improved survival as compared to radiation therapy and/or chemotherapy, while neoadjuvant radiation improves the outcome in locally advance tumours.

Pathologic stage is the most important prognostic parameter for squamous cell carcinoma. The tumours are staged using the TNM system as for urothelial carcinoma. In a series of 154 patients, overall 5-year survival was 56%; for those patients with organ-confined tumour (pT1, 2) it was 67% and for non organ-confined (pT3, 4) it was only 19%.

There are no uniformly accepted criteria for grading of squamous cell carcinoma. Squamous cell carcinoma of the bladder has been graded according to the amount of keratinization and the degree of nuclear pleomorphism.[79]

Verrucous carcinoma is an uncommon variant of squamous cell carcinoma that occurs almost exclusively in patients with schistosomiasis, accounting for 3% to 4.6% of bladder cancers. It has a good prognosis.[23]

Sqamous cell papilloma of the urinary bladder is a very rare benign, proliferative squamous lesion. It occurs in elderly women without specific clinical symptoms. It is not associated with human papilloma virus infection.[23]

1-2-6-3 Adenocarcinoma:

This is defined as a malignant neoplasm derived from the urothelium showing histologically pure glandular phenotype.

Bladder adenocarcinoma is an uncommon malignant tumour accounting for less than 2% of all the malignant urinary bladder tumours. It includes primary bladder adenocarcinoma and urachal carcinoma. It occurs more commonly in males than in females at about 2.6:1, and affects adults with the peak incidence in the six decade of life.[81]

Macroscopically, the tumour may be exophytic, papillary, sessile, ulcerating, or infiltrating and may exhibits a gelatinous appearance.[23]

The cytological features of adenocarcinoma, whether primary or metastatic, includes acinar groups and papillary clusters of vacuolated malignant cells with prominent nucleoli.[82]

Histologically, pure adenocarcinoma of the bladder may show different patterns of growth. These include: enteric (colonic) type, adenocarcinoma not otherwise specified, signet ring cell, mucinous (colloid), clear cell, hepatoid, and mixed. It is not uncommon to find a mixture of these growth patterns. There is no generally accepted grading system ascribed to adenocarcinoma of the bladder.[23]

The immunohistochemical profile of these tumours that has been reported in the literature is variable and closely matches that of colonic adenocarcinoma. Reports of cytokeratin (CK) 7 positivity are variable ranging from 0-82%, while CK-20 is reported to be positive in most bladder adenocarcinomas. Villin has recently been reported to be positive in enteric type adenocarcinoma of the urinary bladder. Another marker of interest is B-catenin, which has been reported to be of help in distinguishing primary adenocarcinoma of the bladder from metastatic colonic adenocarcinoma. Secondary involvement is much more common than the primary adenocarcinoma of the bladder.[23]

Most cases of adenocarcinoma of the urinary bladder are associated with longstanding intestinal metaplasia of the

urothelium, such as may be seen in a non-functioning bladder, obstruction, chronic irritation, and cystocele. Adenocarcinoma arising in exrophy is felt to be secondary to the longstanding intestinal metaplasia common to this disease. The risk of development of adenocarcinoma in extrophy is in the range of 4.1-7.1%. Cystitis glandularis is present in invasive adenocarcinoma ranging from 14-67% of cases, but its role in the pathogenesis of invasive adenocarcinoma is not clear. Adenocarcinoma may also arise in conjunction with villous adenoma, S. haematobium infection, and endometriosis of the bladder.[23]

1-2-6-4 Small cell carcinoma:

Small cell carcinoma (SCC) is a malignant neuroendocrine neoplasm derived from the urothelium which histologically mimics its pulmonary counterpart.[23]

Most if not all, show markers of epithelial differentiation, and the majority apparently produce very small amounts of polypeptides. Pure SCC are rare: less than 1 per cent of all urothelial neoplasms. Signs and symptoms do not differ from those of TCC. Evidence of systemic production of neuroendocrine polypeptides is unusual, even though some type of polypeptide can be identified in the cells of almost all tumours. Small cell carcinomas are often metastatic at the time of clinical detection.

The most common locations for disease spread include: regional lymph nodes, 56%; bone, 44%; liver, 33%; and lung, 20%.[23]

Choong NW, Quevedo JF, Kaur JS performed a retrospective study at Mayo Clinic (Rochester,Minnesota, USA) to characterize the clinical and pathologic features of patients with SCC of the urinary bladder diagnosed between 1975 and 2003. Forty-four patients were identified who had primary bladder small cell carcinoma, 61.4% of whom had pure SCC. The male: female ratio was 3:1, the mean age was 66.9 years, and the mean follow-up was 3.2 years. Twelve patients (27.3%) had stage II disease, 13 patients (29.6%) had stage III disease, and 19 patients (43.2%) had stage IV disease. The overall median survival was 1.7 years.[83]

Almost all the SCCs of the urinary tract arise in the urinary bladder. The tumour may appear as a large solid, isolated, polypoid, nodular mass with or without ulceration, and may extensively infiltrate the bladder wall.

Histopathologically, they consist of small, rather uniform cells, with nuclear molding, scant cytoplasm and nuclei containing finely stippled chromatin and inconspicuous nucleoli. Mitoses are present and may be frequent. Necrosis is common. Roughly 50% of cases have areas of urothelial carcinoma and exceptionally, squamous cell carcinoma and/or adenocarcinoma. This is important, because

the presence of these differentiated areas does not contradict the diagnosis of SCC.

The neuronal-specific enolase is expressed in 87% of cases, and chromogranin A only in a third of cases. The diagnosis of SCC can be made on morphologic grounds, even if neuroendocrine differentiation can not be demonstrated.

This tumour is charachterized by an aggressive clinical course with early vascular and muscle invasion. The overall 5-year survival rate for patients with small cell carcinoma of the bladder with local disease has been reported as low as 8%.[23]

1-2-6-5 Sarcomatoid carcinoma:

Sarcomatoid carcinoma (spindle-cell, metaplastic) carcinoma is a high-grade neoplasm of the bladder in which a malignant epithelial component, clearly identifiable as such (of transitional, glandular, squamous, or undifferentiated type) coexists with areas having a sarcoma-like appearance. The later may have a non-specific spidle-cell or pleomorphic look (sometimes admixed with osteoclast-like giant cells) or may exhibit specific features of mesenchymal differentiation, such as rhabdomyosarcoma, chondrosarcoma, osteosarcoma, liposarcoma, or malignant fibrous histocytoma. When such specific features are present, the tumour may be designated as carcinosarcoma. Whether areas of specific

mesenchymal differentiation occur or not, transitions may be seen between the two major components, suggesting that the sarcoma-like areas are also of epithelial nature. Further evidence of the epithelial nature of these proliferations is provided by the immunoreactivity for keratin often detected in the sarcoma-like component.[18]

Another bladder malignancy charachterized by the presence of heterologous elements is the rare transitional cell carcinoma having areas with morphologic and immunohistochemical features of choriocarcinoma and sometimes accompanied by serum elevation of HCG.[18]

1-2-6-6 None-urothelial tumours:

Any mesenchymal lesion can occur in the urinary bladder and a great many histologic varieties have been recorded. These neoplasms constitute less than 1 per cent of all bladder tumours, and their rarity impedes the accumulation of sufficient information to permit an adequate understanding of their etiology, pathogenesis, and behavior.[43]

In many cases, mesenchymal tumours occupy so much of the pelvis at diagnosis that their site of origin cannot be firmly established. Although mesenchymal tumours occur in the bladder,

there is apparently nothing about their pathology or behavior that is peculiar to their origin.[43]

1-2-6-7 Malignant mesenchymal tumours:

Malignant mesenchymal tumors, although commonly classified according to their predominant histologic differentiation, often present as bulky pelvic masses composed of primitive mesenchymal elements intermixed with cells differentiating toward a variety of soft tissue structures. The exact cell type of origin may be difficult to determine, and many authorities believe that these neoplasms differentiate along multiple lines from multipotential stem cells. Prognosis depends more on patient age and the extend of the cancer than on histologic subtype; separation into high and low grade on the basis of mitoses and nuclear pleomorphism is often the pathologist's most important contribution. These tumours constitute less than 0.5 per cent of all bladder cancers, and descriptions of their characteristics must contain generalizations gleaned from isolated case reports and small series with limited follow-up.[43]

Most malignant mesenchymal tumours have histologic features of muscle differentiation and can be considered myosarcomas. In infants and children, these neoplasms usually occur as large pelvic masses associated with obstruction of urinary outflow from the

ureters and/or urethra. Cases have been reported in association with multiple congenital anomalies of the brain as well as nephroblastomas. Other cases have occurred in fetuses. The disease affects males more often than females in a ratio of 3:1. The predominant histologic subtype in children is embryonal rhabdomyosarcoma. Grossly, these tumors may arise anywhere in the bladder, but they usually involve the base where they appear as discrete polypoid masses with glistening, pale gray surfaces. When this configuration resembles a bunch of grapes, the term botryoid sarcoma has been used. Histologically, edematous masses of stellate, round, and spindle tumor cells infiltrate the lamina propria and muscular wall and elevate the overlying intact urothelium. Cellular density is variable, but cytoplasm is uniformly scanty. Cross-striations are distinctly rare. Nuclei are small but may vary considerably in shape. Chromatin distribution and granularity, as well as the prominence of the nucleoli and mitoses, depend on the differentiation of the cells, and these features are often variable within any individual tumor. Myosarcomas of the bladder in children tend to grow locally rather than to metastasize and have high frequencies of recurrence unless widely excised. Prognosis varies with the extent of invasion at initial diagnosis and adequacy of surgical excision. The eventual outcome is

increasingly favorable and several patients have survived more than 20 years.

Myosarcomas in adult bladders usually present with gross hematuria rather than obstruction. Most are located at the bladder base in men (sex ratio, 2:1) aged 40 to 60 years. The predominant histologic subtype is leiomyosarcoma, and neoplasms tend to be more localized, smaller, better differentiated, and more amenable to partial cystectomy than their childhood counterparts. Tumours are poorly circumscribed and invasive, with ulcerated surfaces. Histologiclly, interlacing bundles of spindle cells are a common pattern, but various degrees of differentiation may occur. Myosarcomas of the adult bladder tend to grow locally but have a higher frequency of metastases (usually hematogenous) than do childhood myosarcomas in this region. The prognosis in most series has been poor. Variations of the common type of adult myocarcomas may occur0.[43]

Osteogenic sarcoma of the urinary bladder has been reported in patient aged 41 to 83 years (mean, 62 years). The disease has occurred almost five times more frequently in men than in women. Gross and microscopic criteria for diagnosis do not differ from those of osteogenic sarcoma at other sites. Like other sarcomas, these tumours tend to grow locally rather than metastasize. In

contrast to carcinosarcomas with bone formation, mixed sarcomas containing osteogenic areas, and epithelial malignancies with osseous metaplasia, pure osteogenic bladder sarcomas have a very poor prognosis, with a 1-year survival rate of approximately 14 per cent.[43]

Malignant fibrous histocytoma (MFH) is one of the most frequent soft tissue sarcomas, and in some series, the second most frequent sarcoma of the urinary tract in adults.[84] It is difficult to determine the incidence of urinary bladder malignant fibrous histocytoma as it is likely that several tumours previously reported as MFH are sarcomatoid urothelial carcinoma. MFH more frequently affects men, and is most common in patients in their 5th to 8th decade. All subtypes of MFH have been described involving the bladder including myxoid, inflammatory, storiform-fasicular, and pleomorphic.[84] Malignant fibrous histocytoma must be separated from the sarcomatoid urothelial carcinoma as well as reactive spindle cell proliferations of the bladder. The much more commonly encountered sarcomatoid urothelial carcinoma can be associated with a malignant epithelial component, and stains positively for the immunohistochemical markers of epithelial differentiation such as cytokeratin. In contrast, malignant fibrous histocytoma is negative for cytokeratin, and can stain for alpha-1-

antichymotrypsin, and CD68. Reactive spindle cell proliferations lack the cytologic atypia of malignant fibrous histocytoma. [75]

Isolated case reports of primary bladder sarcomas include malignant peripheral nerve sheath tumour, hemangiopericytoma after exposure to polyvinyl alcohol, myxoid liposarcoma, malignant mesenchymoma, gangilioneuroma, angiosarcoma, and malignant varieties of predominantly benign lesions such as granular cell tumor.

1-2-6-8 Haematopoitic and lymphoid tumours:

Malignant lymphoma is a malignant lymphoid neoplasm which may occur in the urinary blader as a primary or part of a systemic disease. It constitutes about 5% of non-urothelial tumours of the urinary tract. More than 90% affects the bladder, constituting less than 1% of bladder neoplasms. Secondary lymphoma of the bladder is common in advanced stage systemic lymphoma, shows a slight male predominance and may occur in children. Primary lymphoma of the bladder and urethra are rare, affect mainly females and occur at median age of 60 years.

Among primary urinary tract lymphomas, low grade MALT lymphoma is the most frequent in the bladder.[85] Reactive germinal centers are consistently present while lymphepithelial lesions occur in only 20% of cases associated with cystitis cystica or cystitis

glandularis. Other bladder lymphomas, like Burkitt lymphoma,T-cell lymphoma, Hodgkin lymphoma and plasmacytomas are very rare.

Among secondary urinary tract lymphoma, diffuse large B-cell lymphoma is the single most frequent histological subtype, followed by follicular, small cell, low grade MALT, mantle cell, Burkitt and Hodgkin lymphoma. Antecedent or concurrent MALT lymphomas in the orbit and stomach, and papillary urothelial tumours rarely occur.[86]

Primary MALT of the urinary tract has an excellent prognosis after local therapy with virtually no tumour-related deaths.Secondary bladder lymphoma as the first sign of disseminated disease is termed nonlocalized lymphoma and secondary lymphoma in a patient with a history of lymphoma is termed recurrent lymphoma. Both secondary lymphomas of the bladder have a worse prognosis (median survival 9years and 0.6 years, respectively), comparable to patients with advanced lymphomas of respective histological type elsewhere.[23]

1-2-6-9 Metastatic tumours and secondary extention in urinary bladder:

These are defined as tumours of the urinary bladder that originate from an extravesical, non-urothelial tract neoplasm. The most frequent locations of metastases are the bladder neck and the trigone.

Metastases or, in most cases, direct extension of colonic carcinomas to the bladder are the most frequent at 21%, followed by carcinomas of the prostate (19%), rectum (12%), and uterine cervix (11%). Much less frequent is metastatic spread to the urinary bladder of neoplasias of the stomach, skin, breast and lung at 2.5-4%.

Some metastatic or secondary tumours such as malignant lymphoma, leukemias, malignant melanomas, or prostatic adenocarcinomas may be diagnosed by routine microscopy. However, tumours with less characteristic histological features, poorly or undifferentiated high grade tumours require immmunhistochemical work-up.

Multifocality and prominent vascular involvement in tumours with unusual morphology should raise suspicion of metastatic tumours.[23]

1-2-7 Tumour spread and staging:

Staging, in addition to grade, is critical in the assessment of bladder neoplasms. The staging system most commonly used is the **TNM classificationof urinary bladder tumours.[23]

Transurethral resection (TURB) of all visible lesions down to the base is required for accurate assessment of depth of tumour invasion.[2]

**TNM classification of carcinomas of the urinary bladder

T - Primary tumour

TX Primary tumour cannot be assessed.

T0 No evidence of primary tumour

Ta Non-invasive papillary carcinoma

Tis Carcinoma in situ: "flat tumour"

T1 Tumour invades subepithelial connective tissue

T2 Tumour invades muscle

T2a Tumour invades superficial muscle (inner half).

T2b Tumour invades deep muscle (outer half)

T3 Tumour invades perivesical tissue.

T3a Microscopically.

T3b Macroscopically (extravesical mass)

T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall

T4a Tumour invades prostate, uterus or vagina

T4b Tumour invades pelvic wall or abdominal wall

N - Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis.

N1 Metastasis in a single lymph node 2cm or less in greatest dimension

N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension

N3 Metastasis in a lymph node more than 5 cm in greatest dimension

M - Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Stage grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a,b	N0	M0
Stage III	T3a,b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1,N2,N3	M0
	Any T	Any N	M1

1-2-8 Treatment:

The treatment for bladder cancer depends on the grade, the stage, and whether the lesion is flat or papillary. For small, localized papillary tumors that are not high grade, the initial diagnostic transurethral resection is all that is done. Patients are closely followed with periodic cystoscopies and urine cytology for the rest of their life for tumor recurrence.

When a patient presents with multifocal bladder tumours, instillation of topical chemotherapy into the bladder, in the immediate postoperative period, can reduce the likelihood of tumor recurrence. Several intravesical chemotherapeutic agents are used e.g. triethylenethiophosphoramide (thiotepa), an alkylating agent, and mitomycin C, an antitumour antibiotic.[87, 88]

After the biopsy site has healed, patient who are at high risk of recurrence and/or progression (CIS; papillary tumors that are high-grade, multifocal, have a history of rapid recurrence, or are associated with lamina propria invasion) receive topical immunotherapy consisting of intravesical installation of an attenuated strain of *Mycobacterium tuberculosis* called Bacillus Calmette-Guerin (BCG). The therapy presumably works by eliciting a local cell-mediated immune reaction that destroys tumor cells.

Several immunotherapeutic agents other than BCG have been investigated for the prophylaxis of superficial bladder cancer, including recombinant IFN-α.[89, 90]

Salvage cystectomy, although associated with significant morbidity, remains a viable form of therapy for patients in whom definitive radiotherapy fails.[91] Radical cystectomy is typically performed for (1) tumor invading the muscularis propria, (2) CIS or high-grade papillary cancer refractory to BCG, and (3) CIS extending into the prostatic urethra and extending down the prostatic ducts beyond the reach of BCG.

Advanced bladder cancer is treated by systemic chemotherapy. New therapeutic procedures are emerging such as photodynamic, laser treatment and gene therapy.[92-95]

1-2-9 Prognostic and predictive factors:

Clinical factors:

In general, individual prognosis of infiltrating bladder tumours can be poorly predicted based on clinical factors alone. Tumour multifocality, tumour size of >3cm, and concurrent carcinoma in situ have been identified as risk factors for recurrence and progression. Tumour extension beyond the bladder on bimanual examination, infiltration of the ureteral orifice, lymph node

metastases and presence of systemic dissemination are associated with a poor prognosis.

Urothelial neooplasms in individuals younger than 20 years more commonly occur in males and are predominantly low grade with a favorable clinical outcome.[96]

Deletion of the ABH and Lewis blood group antigens appears to correlate with an aggressive clinical course, in the form of increased probability of recurrence and the acquisition of invasive features.

Morphologic factors:

Morphologic diagnostic factors include grade, stage, as well as other specific morphologic features. Histologic grade probably has prognostic importance for pT1 tumours. As most pT2 and higher stage tumours are high grade, its value as an independent prognostic marker remains questionable. In long-term programs, D. Ramos, et al demonstrated that PUNLMP have a low recurrence rate and a minimal risk for tumour progression in comparison with papillary urothelial carcinoma, low grade.[97]

Depth of invasion, which forms the basis of pT categorization, is the most important prognostic factor. In efforts to stratify category p T 1 tumours further, sub-staging systems have been proposed on the basis of the level of invasion into the lamina

propria. Tumours that infiltrate beyond the muscularis mucosa have a higher progression rate. Carcinoma in situ is more frequent with increasing grade and stage of the associated tumour, and carcinoma in situ with microinvasion seems to increase the propability of aggressive behaviour. Lymphatic and/or vascular invasion is associated with decreased survival in pT1 tumours (44% 5-year survival).

Specific subtypes or histologic variants of urothelial carcinomas such as small cell carcinoma, sarcomatoid carcinoma, nested variant, micropapillary carcinoma, and lymphoepithelioma-like carcinoma may be clinically relavent in patient's prognosis. Margin status after cystectomy is also an important predictor of prognosis. The pattern of tumour growth has been suggested to be important; a pushing front of invasion had a more favourable prognosis than tentacular invasion in few studies.

Genetic factors:

Despite marked differences in the prognosis of pT1 and pT2-4 cancers, these tumours are highly similar on the genetic level. It could therefore be expected, that similar genetic alterations might be prognostically relevant in all stages. A multitude of molecular features has been analyzed for a possible prognostic role in invasively growing bladder cancer. Despite all this extensive

research, there is currently no molecular parameter that is sufficiently validated and has sufficient predictive power to have accepted clinical value in these tumours.

The nuclear overexpression of p53, as detected immunohistochemically and as a likely indicator of a mutation, has been found to show a high statistical correlation with disease progression in T1 bladder carcinomas. Both grade and stage of bladder carcinoma seems to be related to this alteration.

Lacombe L, et al in their study concluded that in the group of patients with residual disease after BCG therapy, p53 status is a better predictor of disease progression than post-BCG stage.[98]

Pfister C, et al studied the prognostic value of Ki-67 index in three hundred nineteen patients with newly diagnosed superficial (pTa, Pt1) papillary bladder tumours and correlate it with the S-phase fraction (SPF) measured by flow cytometry. They found that the frequency of high Ki-67 expression (> or = 10%) increased with stage (P=.005) and grade (P=.001), but not with tumour size or multifocality. Tow hundred one patients experienced tumour recurrence in a median follow-up of 68 months. Ki-67 index greater than 10% was found to be independent predictor of tumour recurrence among patients with tumours larger than 3 cm in diameter, but not those with smaller size tumours.With regard to

the DNA index, they observed a significant but weak correlation between Ki-67 expression and the SPF (Spearman's correlaton coefficient=0.23, P=.004). In addition, they found that aneuploid tumours had significantly higher expression of Ki-67 (2205%) than diploid tumours (10.1%) (P=.0006). Moreover, patients with DNA aneuploid bladder tumours were more likely to have more than 10% Ki-67-positive cells than those with diploid tumours. They concluded that in patients newly diagnosed superficial (pTa, pT1) bladder tumours, a Ki-67 index above 10% is an independent predictor of shorter time to recurrence only in those with tumours larger than 3 cm.[99, 100]

1-3 OBJECTIVES

1-3-1 General objectives:

To study the pattern of urinary bladder neoplasms among Sudanese patients diagnosed at Ibn Sina Hospital, Suba Teaching Hospital, and The National Health Laboratory; from January 2004 through to December 2005 with view to determine epidemiological and clinicopathological features of this malignancy.

1-3-2 Specific objectives:

1- To determine the histopathological pattern of urinary bladder neoplasms among Sudanese patients.

2- To determine the age, sex, residency distribution, and clinical presentation of urinary bladder neoplasms in the studied group.

3- To establish the association of urinary bladder neoplasms with tobacco smoking, industrial occupation, use of analgesics and medicinal drugs, and schistosomaisis as risk factors in Sudanese patients.

4- To determine the common diagnostic procedures used for the diagnosis of urinary bladder neoplasms among Sudanese patients.

5- To verify different therapeutic options and the outcome of urinary bladder neoplasms among the studied group.

2- METHODOLOGY

2-1- Study design:

This is a descriptive retrospective study.

2-2- Study field:

The study was carried out at Ibn Sina Hospital, Soba University Hospital and the National Health Laboratory at Khartoum, Sudan.

Ibn Sina Hospital is a specialized hospital for renal and gastrointestinal diseases. It receives patients from different regions of Sudan for diagnosis and management.

Soba University Hospital is a teaching hospital that belongs to University of Khartoum.

The National Health Laboratory stands as a national reference laboratory located at the centre of Khartoum. It receives samples from different parts of Sudan. It has several departments including histopathology department. It contains the Cancer Research Centre of Sudan.

2-3- Study population:

All cases of urinary bladder neoplasms (UBN) presented to Ibn Sina, Soba University hospitals or the NHL from January 2004 through to December 2005.

2-4- Inclusion criteria:

Patients of (UBN) who were diagnosed histopathologically at the three above mentioned centres with or without urine cytology and radiological studies.

2-5- Exclusion criteria:

1- Urinary bladder neoplasms patients who had no histopathological slides in the histopathology lab of Ibn Sina and Soba Hospitals or the NHL were excluded from this study.

2- Poorly stained slides were excluded from the study.

3- Any case with no adequate information was also excluded.

2-6- Materials and methods:

Data were collected from the patient's request forms in a predesigned questionnaire with detailed history and investigations. Cystoscopic findings were collected from cystoscopic reporting files in the Cystoscopy Unit in Ibn Sina Hospital and from the genitourinary cards (GU cards) in Soba Hospital. Patients studied in the year 2005 were interviewed directly especially for risk factors while patient's files were referred to for those studied in the year 2004. The histopathological slides of patients included in the study were collected and reviewed by

experienced histopathologist to confirm the UBN diagnosis; determine the histopathological type of the tumour; and classify the UBN using the WHO and the WHO/ISUP grades.

Microscopic pictures were obtained using Olympus BX 51 and DP 70 video-microscopy system in the NHL.

2-7- Statistics:

The data were electronically analyzed using computer S.P.S.S. program, version 10.

3- RESULTS

There were 141 patients with UBN diagnosed at Ibn Sina Hospital (ISH), Soba University Hospital, and the NHL during the two years of the study. When the slides were reviewed, 35 had no available slides or information and so were excluded from this study. The remainders (106 cases) were analysed.

During the two-year study, 101 UBN patients were admitted to ISH, 95 patients of them were diagnosed at ISH histopathology laboratory (4.5% of the total histopathology samples received during 2004 & 2005 in ISH histopathology laboratory), and those included in the study were 66 patients.

Forty-nine patients were admitted to SUH during the two-years of the study, 32 were diagnosed at SUH histopathology lab (1.3% of the total histopathology samples received during 2004 & 2005 in SUH histopathology laboratory), and 31 of them were included in the study.

In the NHL, 14 UBN cases were diagnosed during the years 2004 and 2005. They represented 0.9% of the total number of

cancer cases registered during this period. 9 cases were included in the study.

3-1- Characteristics of the studied patients:

3-1-1- Age distribution:

The ages of the studied patients ranged from 18-90 years with a mean of 59.49 ± 13.73. Nine (9%) patients were below 40 years of age. The youngest patient was 18 years old. The peak age of incidence was 60-< 80 years (Figure 1).

3-1-2- Sex distribution:

Eighty-seven (82.1%) patients were males compared to nineteen (17.9%) females (Figure 2).Sixty-two of the seventy-two TCC cases were males and ten were females, whereas eighteen out of the twenty-six SQCC cases were males and eight were females. As a result of these findings, the male to female incidence rate ratio (R.R) for TCC was 6.2:1 and for SQC was 2.3:1. For all UBN it was 4.6:1(Table 1).

The peak incidence rate for males was at the age of 60-<80, while females had two peaks, one at the age group 40-<60, and the other at the age group 60-<80 (Figure 3).

3-1-3- Geographical distribution of UBN in the studied patients:

As regard to origin, twenty-six (37.1%) patients were originally from the North of Sudan, seventeen (24.3%) from Central Sudan, twenty-five (35.7&) from the West, two (2.9%) from the East, and no one was from the South of Sudan (Figure 4).

Concerning residency, thirty-six (50%) patients were from Khartoum, twenty (27.8%) patients from Omdurman, and sixteen (22.2%) were from Khartoum Bahri.

3-1-4 Occupational distribution of UBN in the studied patients:

Twenty-four (44.4%) patients were found to be labourer, 10 (41.7%) of them were farmers. Sixteen (29.6%) patients were housewives (all females), six (11.1%) employee, three (5.6%) free workers, two (3.7%) students, and three (5.6%) patients were of other occupations.

3-1-5- Ethnic distribution of the studied patients:

Thirty-three (41.5%) patients were from tribes of the North region of Sudan. Among them, Gaaleen tribe has the highest incidence of UBN (27.3%). Twenty-six (38.2%) from tribes of the

West, five (7.4%) from Central region, four (5.9%) from East tribes, and no patient was from the South region of Sudan .

3-2- Distribution of risk factors in the studied patients:

Table 2 shows risk factors of UBN in the studied patients. Eighteen (43.9%) out of forty-one patients had history of tobacco smoking and sixteen (38.1%) out of forty-one patients give positive history of urinary shistosomaisis. No history of industrial occupation, use of analgesics, or medicinal drugs in the studied patients.

Fourteen (53.8%) out of 26 TCC cases were smokers, while twelve (46.25) were not smokers (P= 0.275). Three (27.3%) out of eleven SQCC had positive history of tobacco smoking and eight (72.7%) had not (P=0.275) (Figure 5).

Eleven (84.6%) out of 13 patients with SQCC had a positive history of urinary shistosomaisis, while two (15.4%) had not. Four (16%) out of 25 patients with TCC had positive history of urinary shistosomaisis and twenty-one (84%) had not (P=0.0001).
(Figure 6)

3-3- Distribution of the clinical presentation of UBN among the studied patients:

Table 3 demonstrates the various presentations of UBN in the studied patients. Gross hematuria was the leading presenting symptom (84%). Microscopic hematuria represented only 3.4% of the presenting symptoms. About 46.1% of patients with UBN presented with other symptoms including suprapubic pain, urine retention, and weight loss.

The duration of symptoms varied from one week to 6 years. Among the total, 52.9% of patients had symptoms <6 months duration, while 47.1% had symptoms of >6 months.

3-4- Distribution of the diagnostic procedure of UBN in the studied patients:

Fifty-three (75.7%) out of 70 patients were diagnosed first radiologically using ultrasonography (U/S), fifteen (21.4%) by cystoscopy and biopsy, while only two (2.9%) were diagnosed first by IVU. None of the patients in the studied group was diagnosed first by urine cytology or CTscan or MRI or surgical resection .

3-5-Cystoscopy findings of UBN in the studied patients:

3-5-1- Localization of UBN in the studied patients:

In eighty studied cases, the location of UBN was as follows: lateral walls, 36 (45%) cases; anterior wall, 5 (6.3%) cases; posterior wall, 4 (5%) cases; dome, 3 (3.8%) cases; neck, 2 (2.5%) cases; ureteric orifices, 2(2.5%) cases; and multiple sites, 28 (35%) cases (Table 4).

3-5-2- Size distribution of UBN in the studied patients:

Twenty-one (25.6%) out of 82 cases showed tumour size of <3cm at presentation, thirteen (15.9%) were 3-6cm, and forty-eight (58.5%) were of >6cm at presentation. Figure 7 shows the relationship between size and grade (WHO/ISUP) of UBN in the studied patients.

3-6-Type of specimens in the studied patients:

Eighty-two (77.4%) of the specimens were TUBPs, eighteen (17%) TURBTs, four (3.8%) cystectomies, one (0.9%) is true-cut needle biopsy, and one (0.9%) specimen is obtained during laprotomy (Table 5).

3-7- Histopathological characteristics of UBN in the studied patients:

3-7-1- Histopathological patterns (diagnosis):

Figure 8 shows the different histopathological patterns of UBN in the studied patients. TCC with its different grades is seen in seventy-two (67.9%) cases (Figures 9-12). Various variants were identified (Figures 13-15). Twenty-six (24.5%) were SQCCs (Figures 16-18), three (2.8%) were TCC with sqamous differentiation (Figure 19), and five (4.7%) others. The other patterns include two adenocarcinoma (Figure 20), liposarcoma (Figure 21), leiomyosarcoma, and malignant fibrous histocytoma (Figure 22).

3-7-2- Configuration of TCC cases in the studied patients:

Thirty-nine (51.3%) out of 76 TCC cases were papillary, nineteen (25%) solid, and eighteen (23.7%) showed both papillary and solid configuration.

3-7-3- Muscle invasion of TCC cases in the studied patients:

There were twenty-eight (36.8%) of the 76 TCC cases with muscle invasion at diagnosis and twenty-one (27.6%) with no muscle invasion, whereas twenty-seven (35.5%) cases contain no muscle to assess invasion in the specimen provided.Figure 23 shows the relationship between muscle invasion and outcome of UBN in the studied patients.

3-7-4- WHO grading of TCC cases in the studied patients:

Forty-four percent of the TCC cases presented at grade III, 30.7% at grade II, 22.7% at grade I, and 2.7% (two cases) graded as papillomas using the WHO (1973) grading system (Table 6).

3-7-5- WHO/ISUP grading of the TCC cases in the studied patients:

There were 43.4% of TCC cases graded as papillary carcinoma of high grade, 52.6% papillary carcinoma of low grade, 1.3% papillary neoplasm of low malignant potential, 1.3% pailloma, and 1.3% (one case) was graded as flat neoplasm using the WHO/ISUP grading system (Table 7).

3-7-6- Differentiation of SQCC cases in the studied patients:

In the current study, twelve (42.9%) were poorly differentiated SQCCs, nine (32.1%) moderately differentiated, and seven (25%) cases were well differentiated SQCCs.

3-7-7- Keratinisation of SQCCs in the studied patients:

Nineteen (67.9%) of the 28 SQCCs were non-keratinized, and nine (32.1%) were keratinized SQCCs.

3-8- Distribution of treatment used in the studied patients:

Twenty-seven (25.5%) of all cases were treated by TURBT alone, 10 (9.4%) TURBT with radiotherapy, 6 (5.7%) TURBT with BCG, 6 (5.7%) received radiotherapy alone, 3 (2.7%) underwent salvage cystectomy with diversion of urine, 2 (1.9%) salvage cystectomy alone, one (0.9%) bypass with radiotherapy, one (0.9%) cystectomy with radiotherapy, one (0.9%) debulking with cyto-dithermy, one (0.9%) urine diversion alone, one (0.9%) radical cystectomy, and two (1.9%) did not receive any treatment (Table 8).

3-9- Outcome of UBN in the studied patients:

Fifteen (46.9%) patients (out of 32 patients followed through the two years of the study) passed because of UBN, twelve (35.5%) were alive and well, four (12.5%) were alive with recurrences, and one (3.1%) was alive and ill (Table 9). Figure 24 shows the relationship between grades and outcome of UBN among the studied patients.

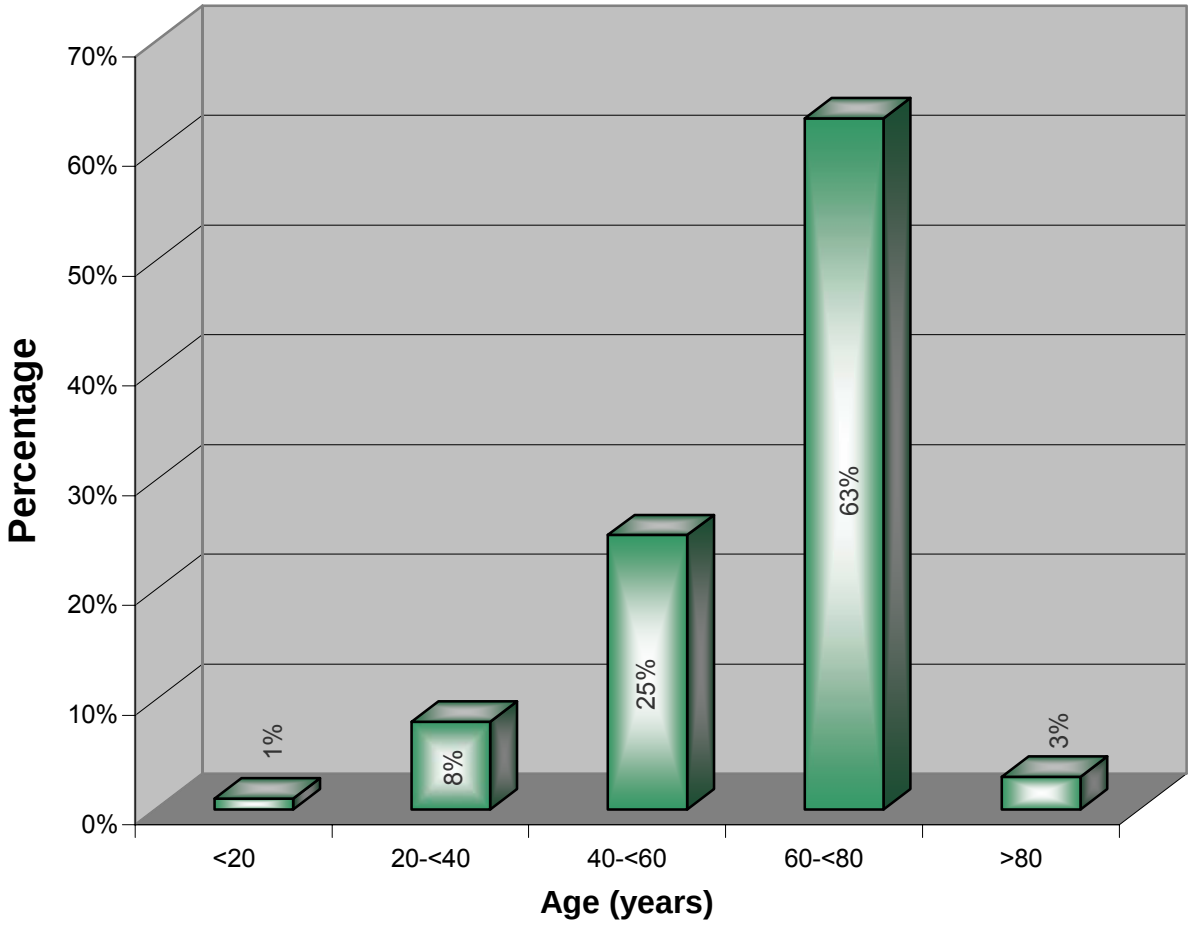


Figure (1): Age distribution in UBN in the studied patients (N = 106)

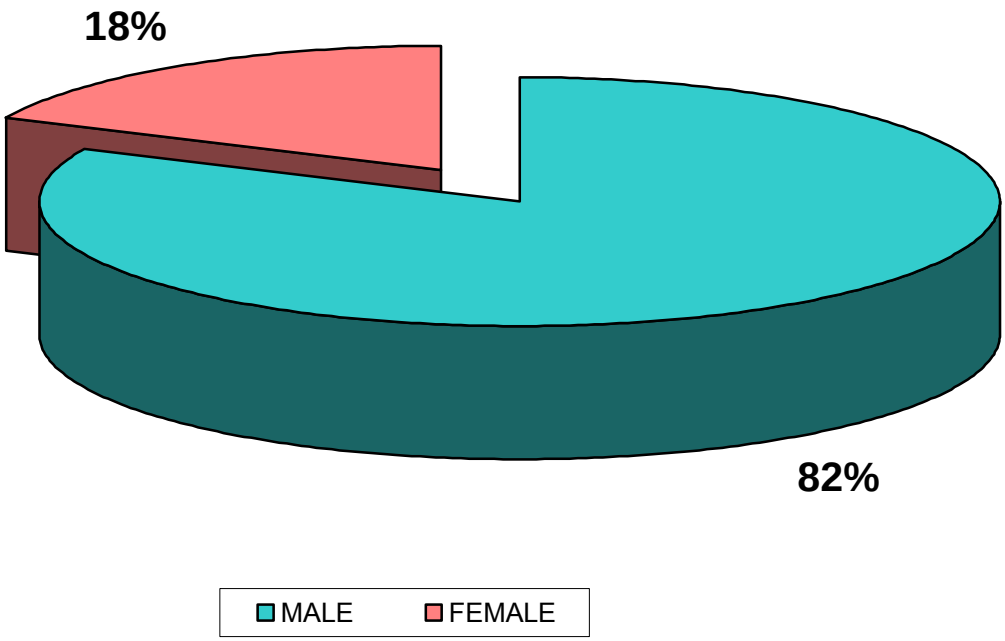


Figure (2): Sex distribution in UBN in the studied patients (N = 106)

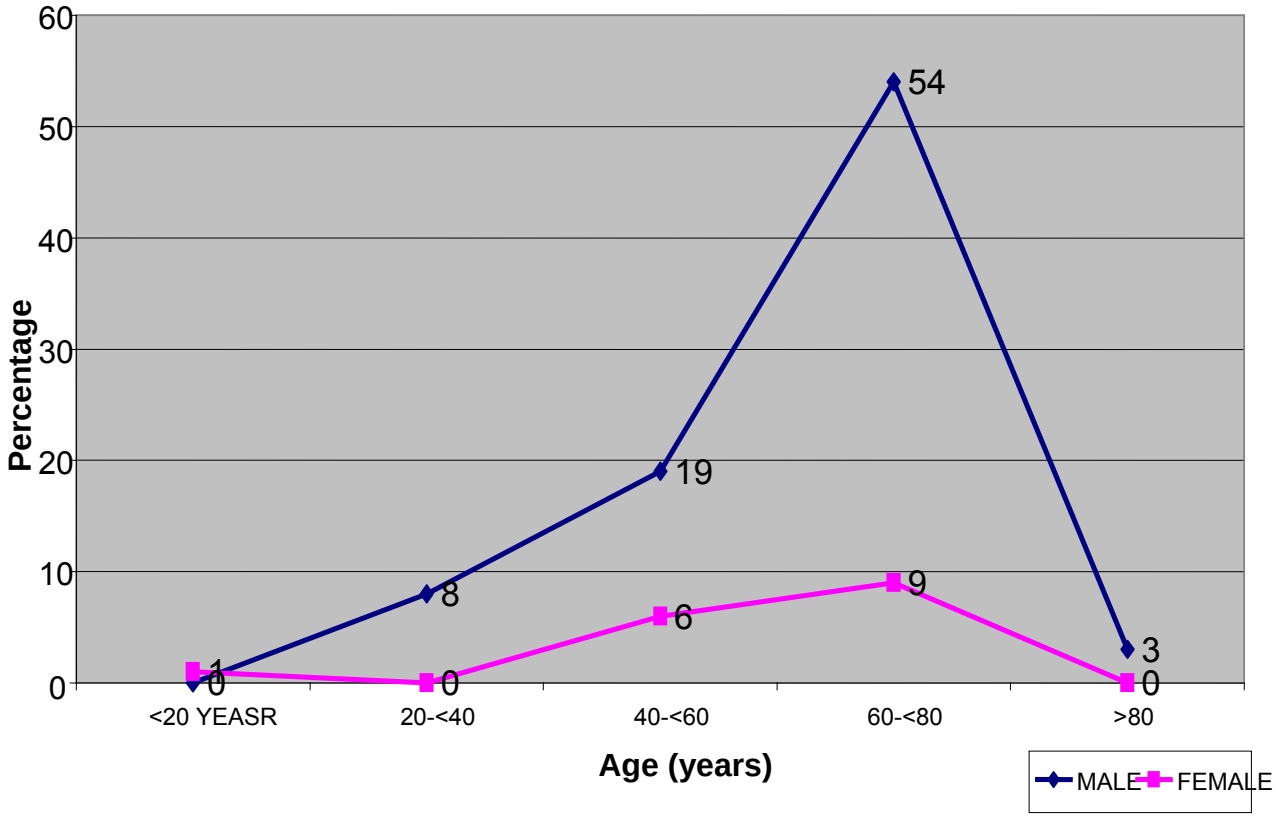


Figure (3): Age specific incidance rate of UBN in males and females among the studied patients (N=106)

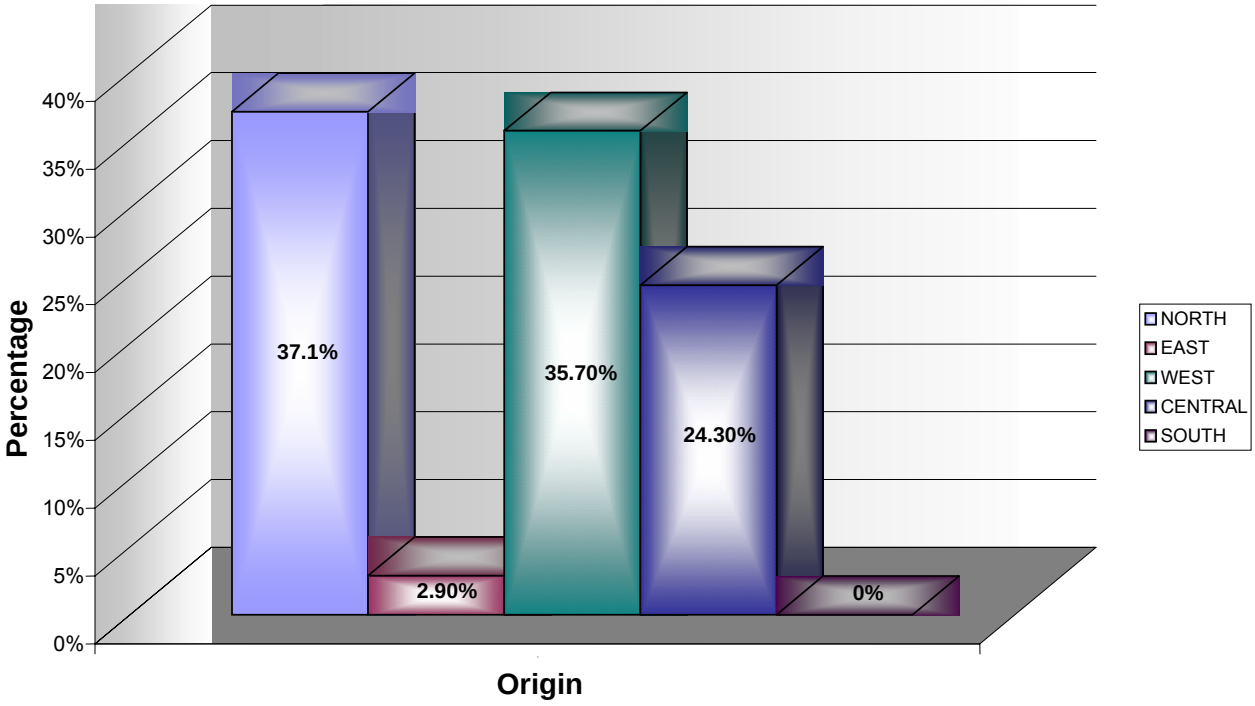
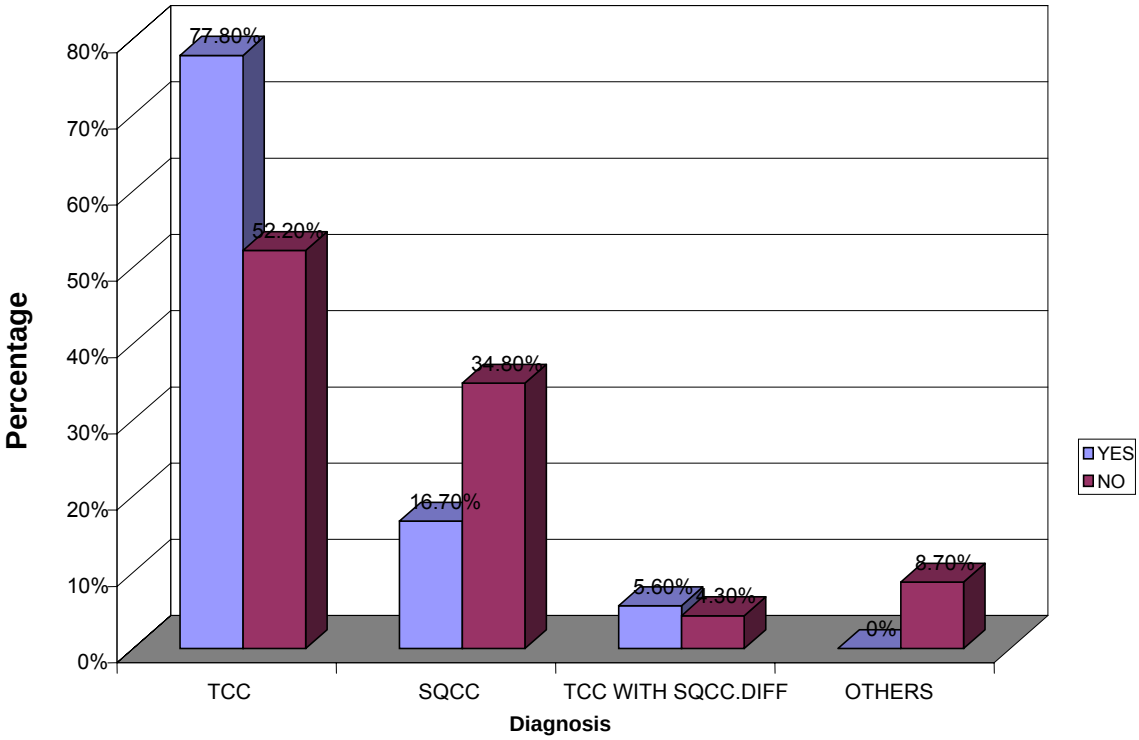


Figure (4): Original distribution of UBN in the studied patients



Fifure (5): Relationship between tobacco smoking and diagnosis of UBN in the studied patients (P=0.275)

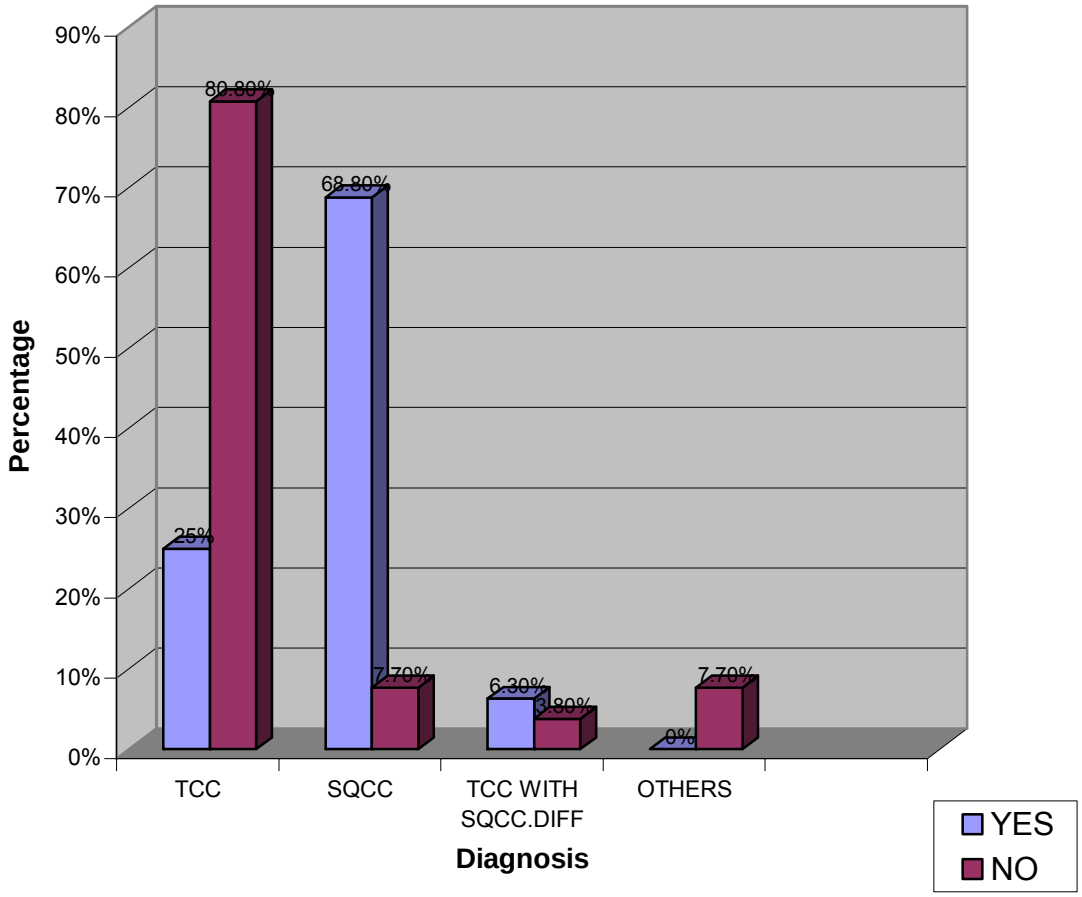


Figure (6): Relationship between diagnosis of SQCC and shistosomiasis among the studied patients (P=0.0001)

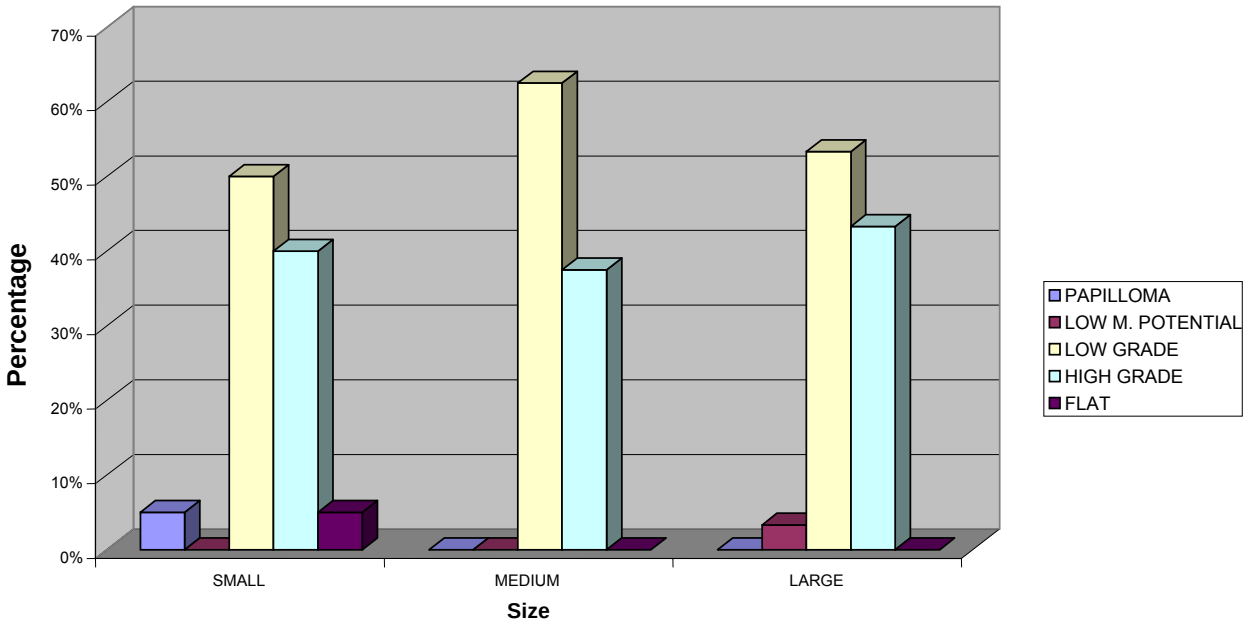


Figure (7): Relationship between size and grade (WHO/ISUP) of UBN in the studied patients (P=0.761)

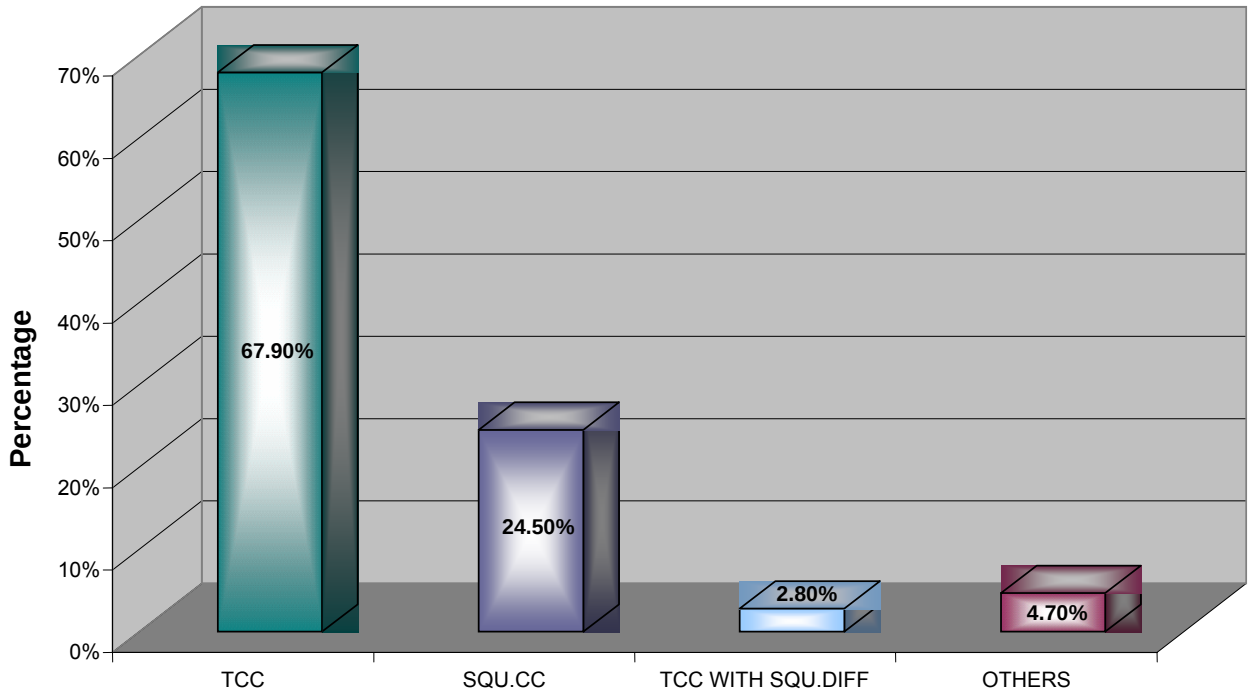


Figure (8): Histological patterns of UBN in the studied patients (N=106)

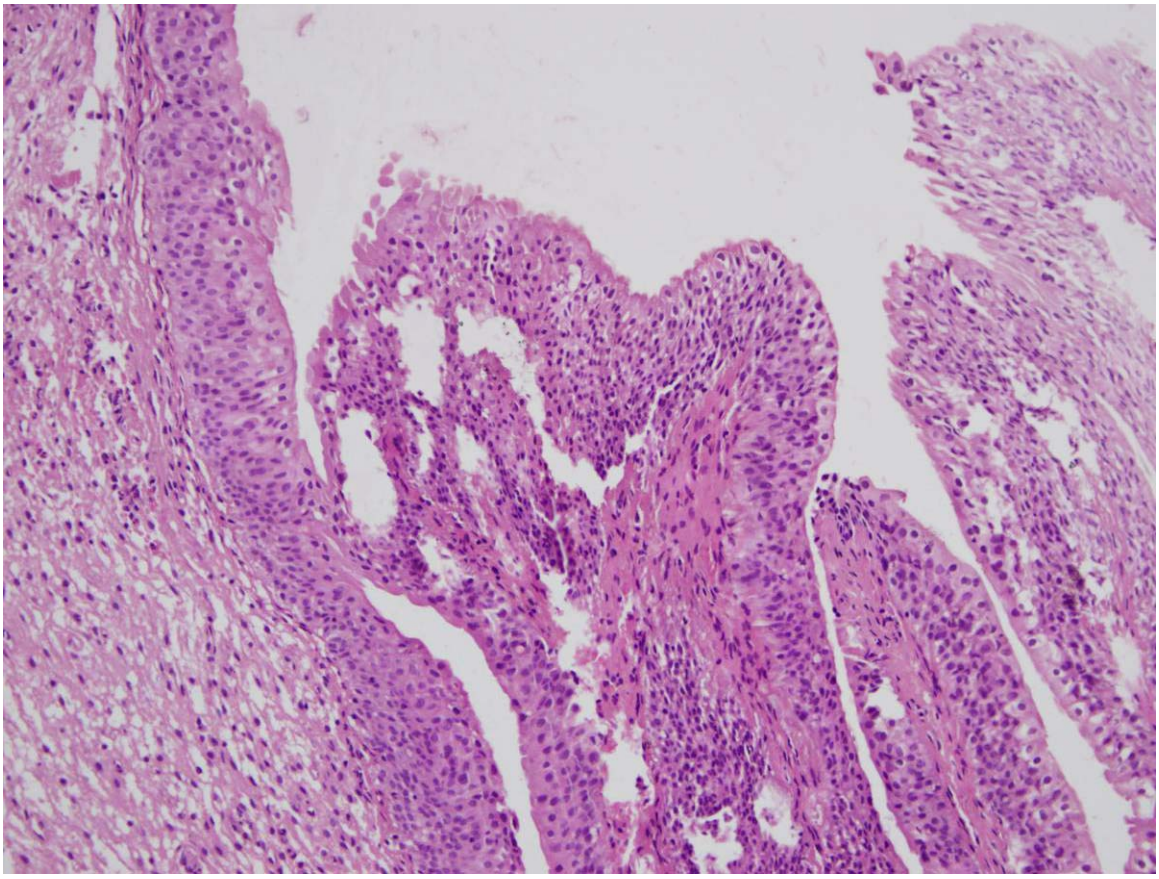


Figure (9): Non-invasive urothelial neoplasm, urothelial papilloma. Discrete papillary fronts, with occasional branching but, without fusion. (H/E. X20)

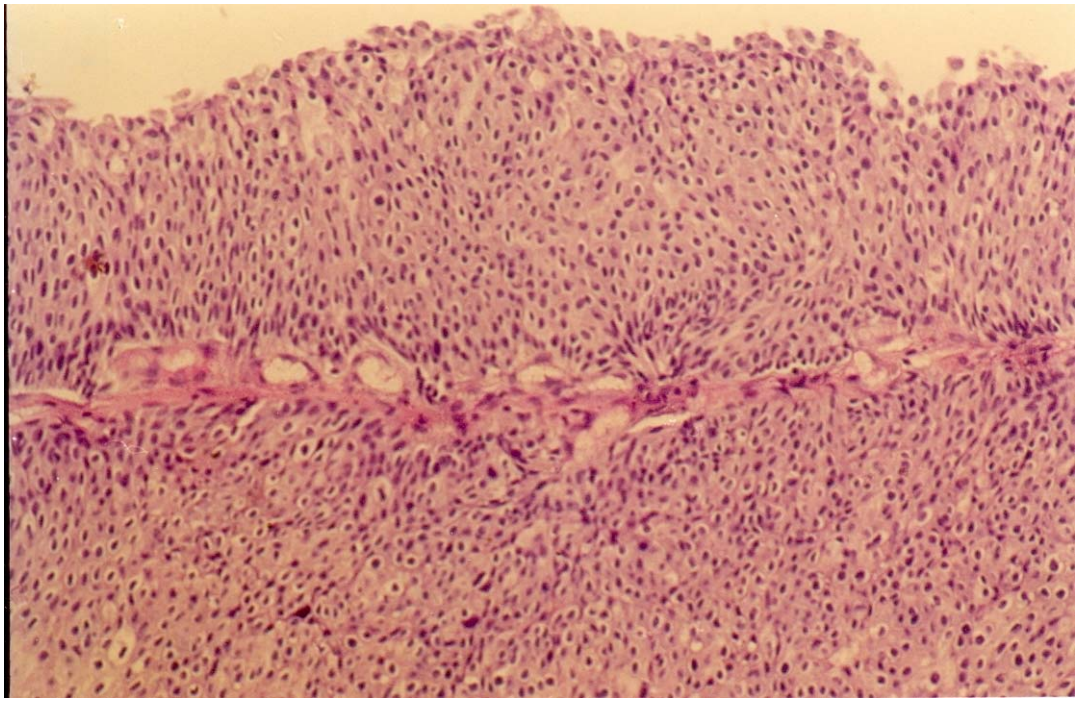


Figure (10): Non-invasive papillary urothelial carcinoma, low grade. Note variation in nuclear polarity, size, shape and chromatin pattern (H&E. X20).

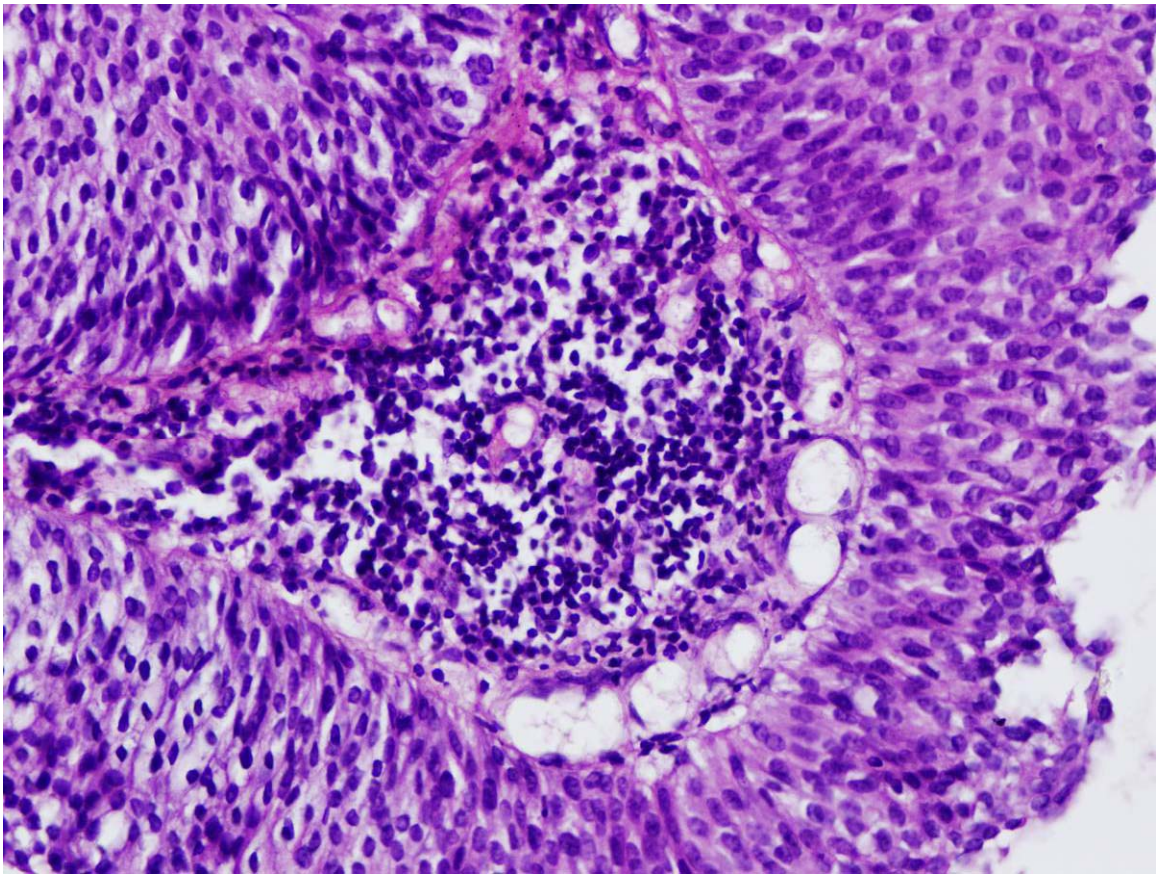


Figure (11): Papillary urothelial carcinoma, low grade with lymphoplasmacytic infiltration in the core (H&E. X20).

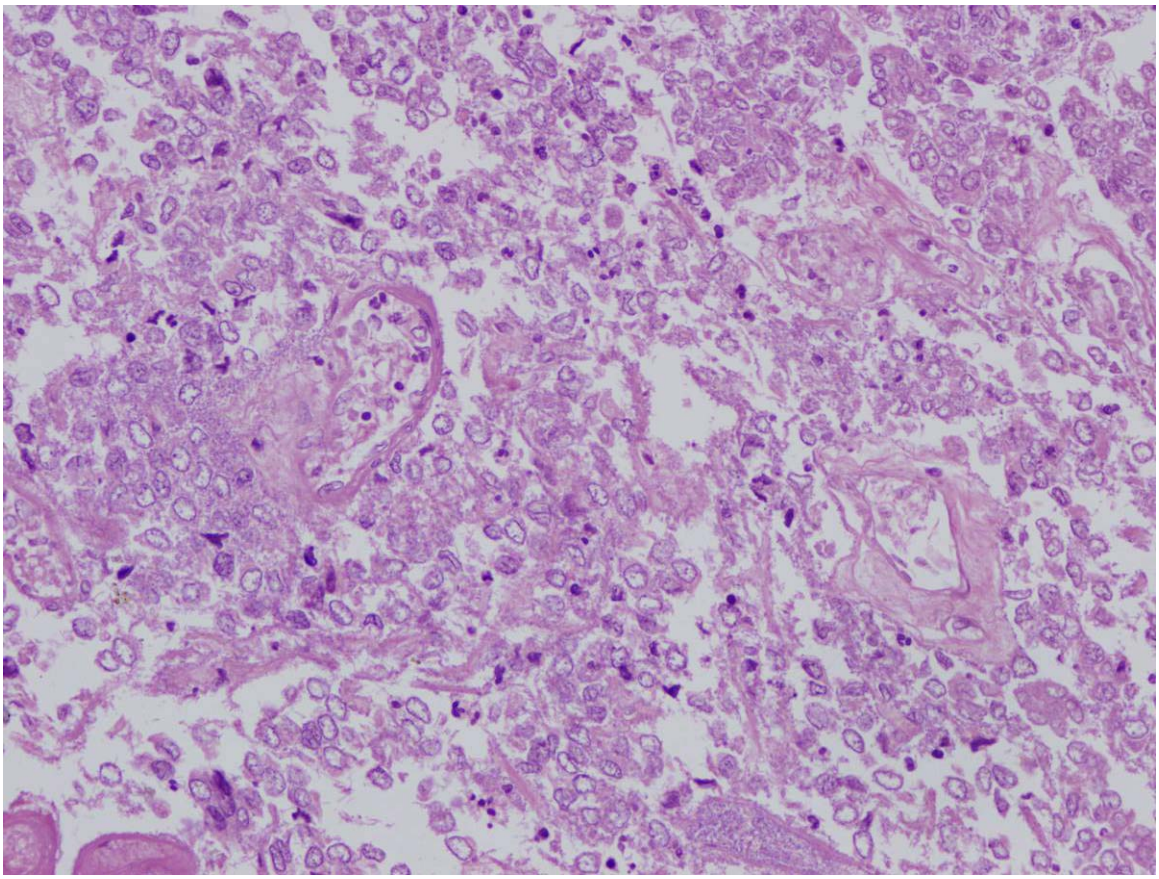


Figure (12): Papillary urothelial carcinoma, high grade. The architecture is disordered and there is marked nuclear pleomorphism, hyperchromasia and necrosis. Mitotic figures are readily visible (H&E. X40).

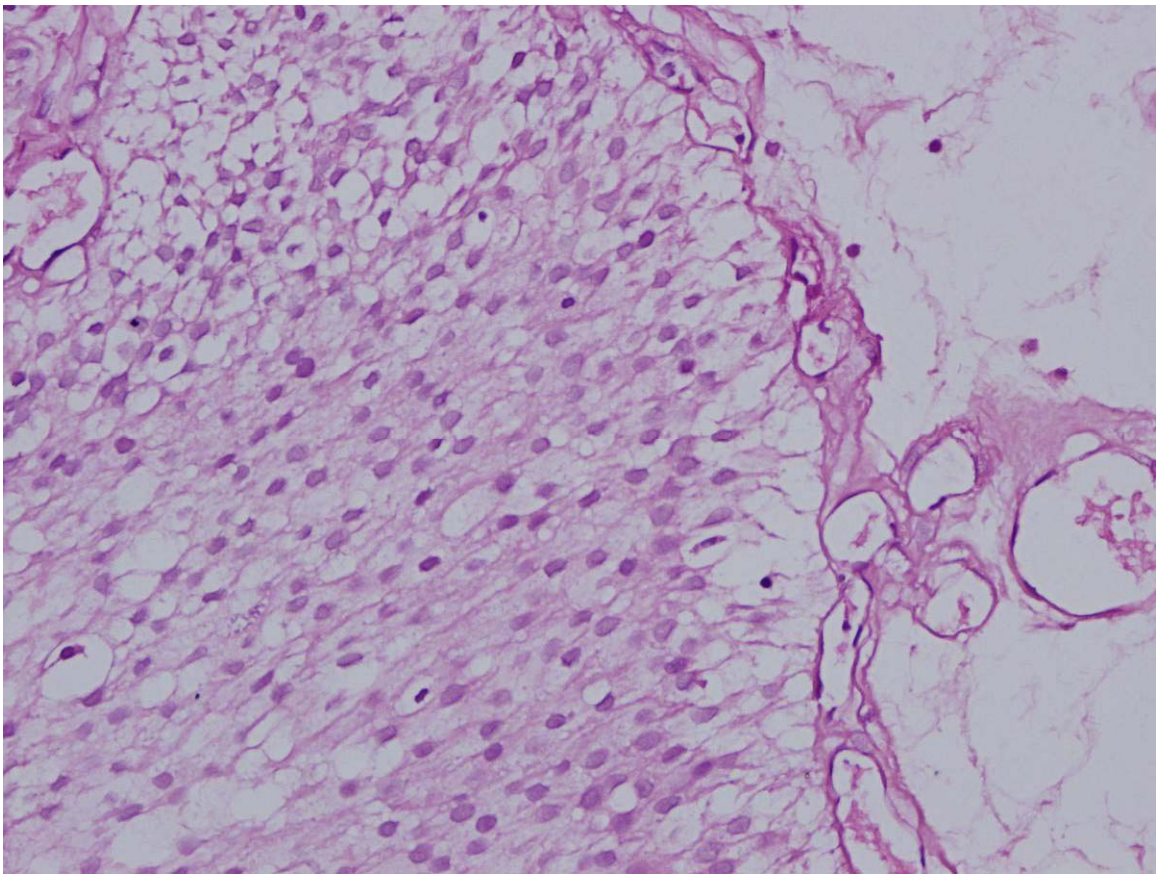


Figure (13): Infiltrative urothelial carcinoma clear cell variant. A clear cell pattern with glycogen-rich cytoplasm is noted (H&E. X40).

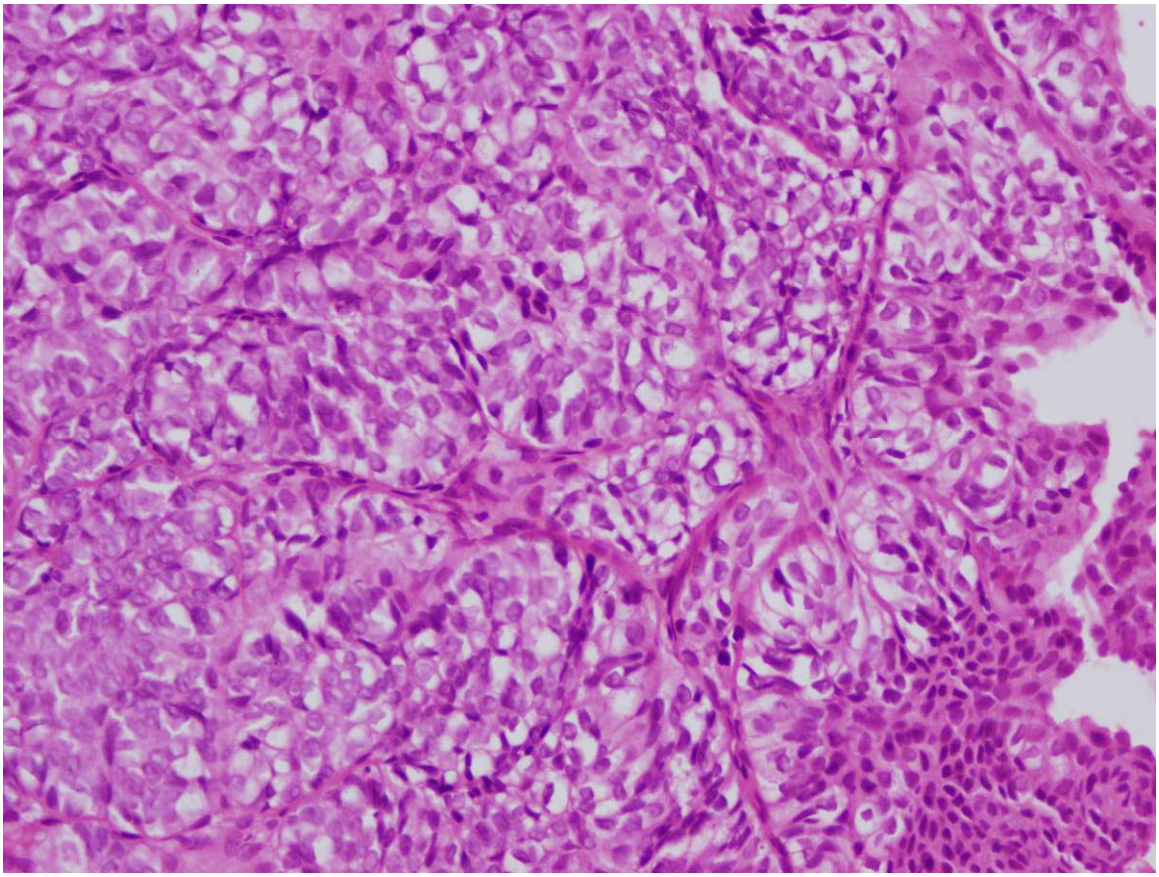


Figure (14): Infiltrative urothelial carcinoma, nested variant (H&E. X40).

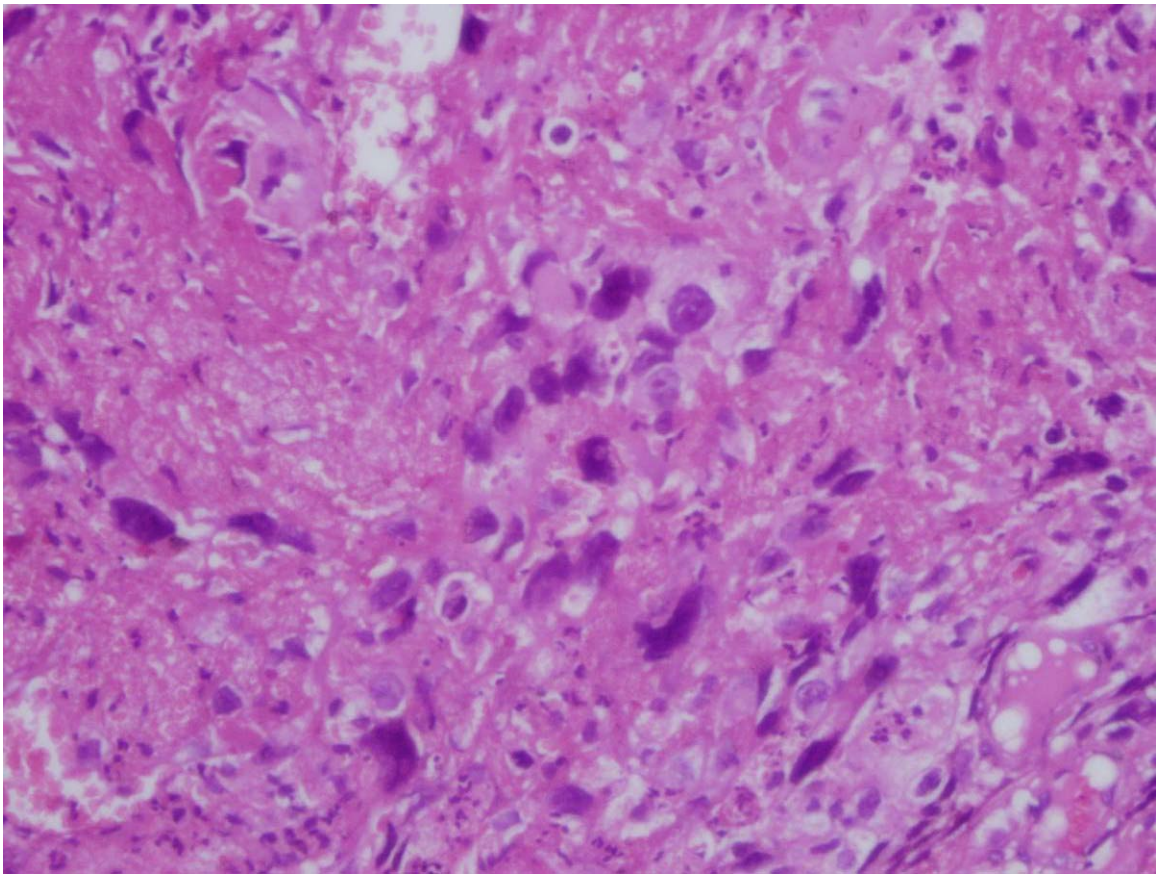


Figure (15): Infiltrative urothelial carcinoma, undifferentiated variant (H&E.X40).

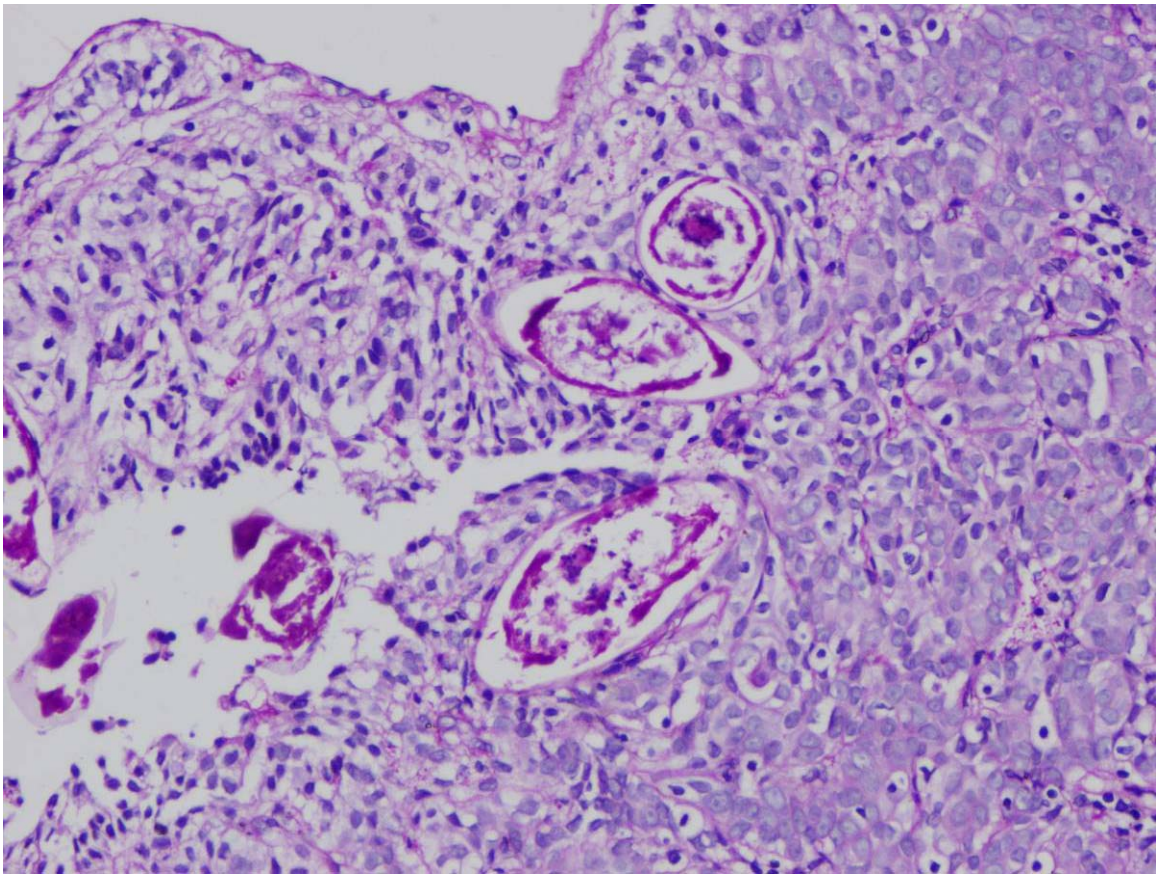


Figure (16): Squamous cell carcinoma with *Shistosoma heamatobium* eggs (PAS.X40).

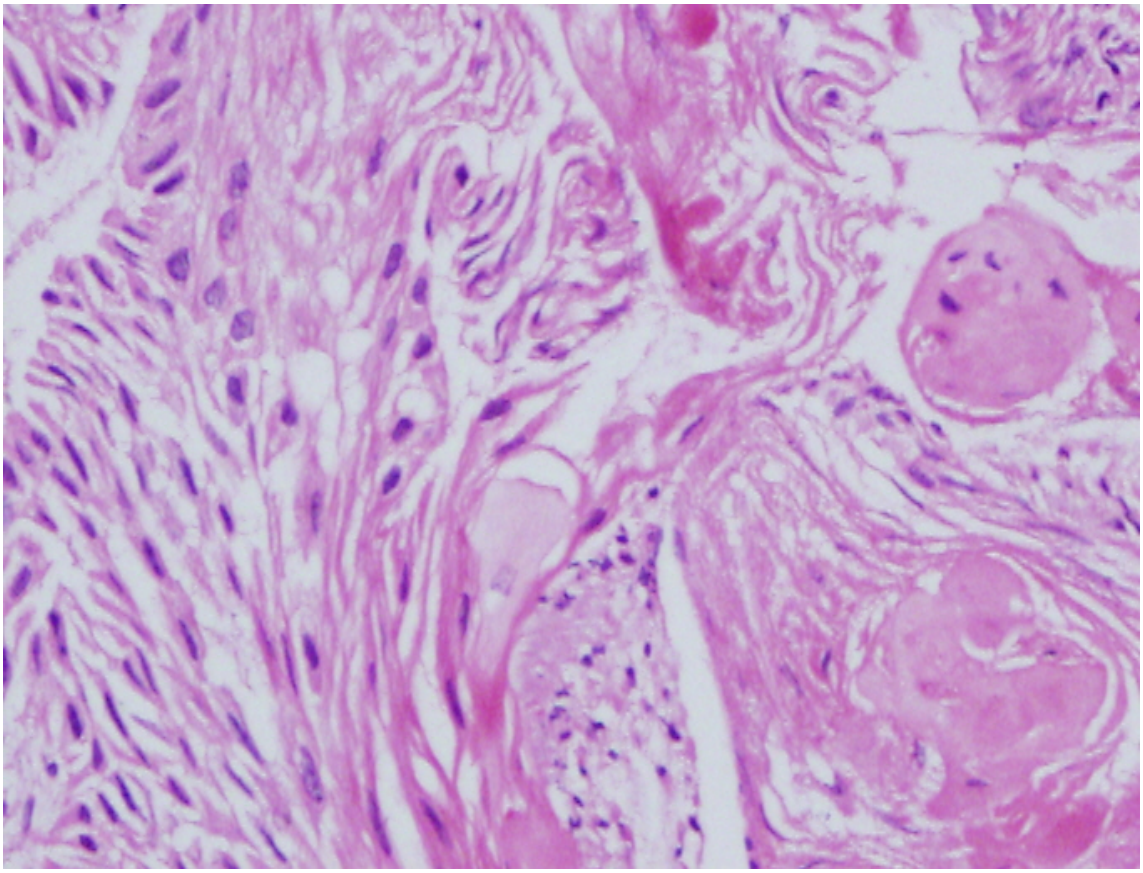


Figure (17): Squamous cell carcinoma of the urinary bladder well differentiated with keratinization (H&E. X40).

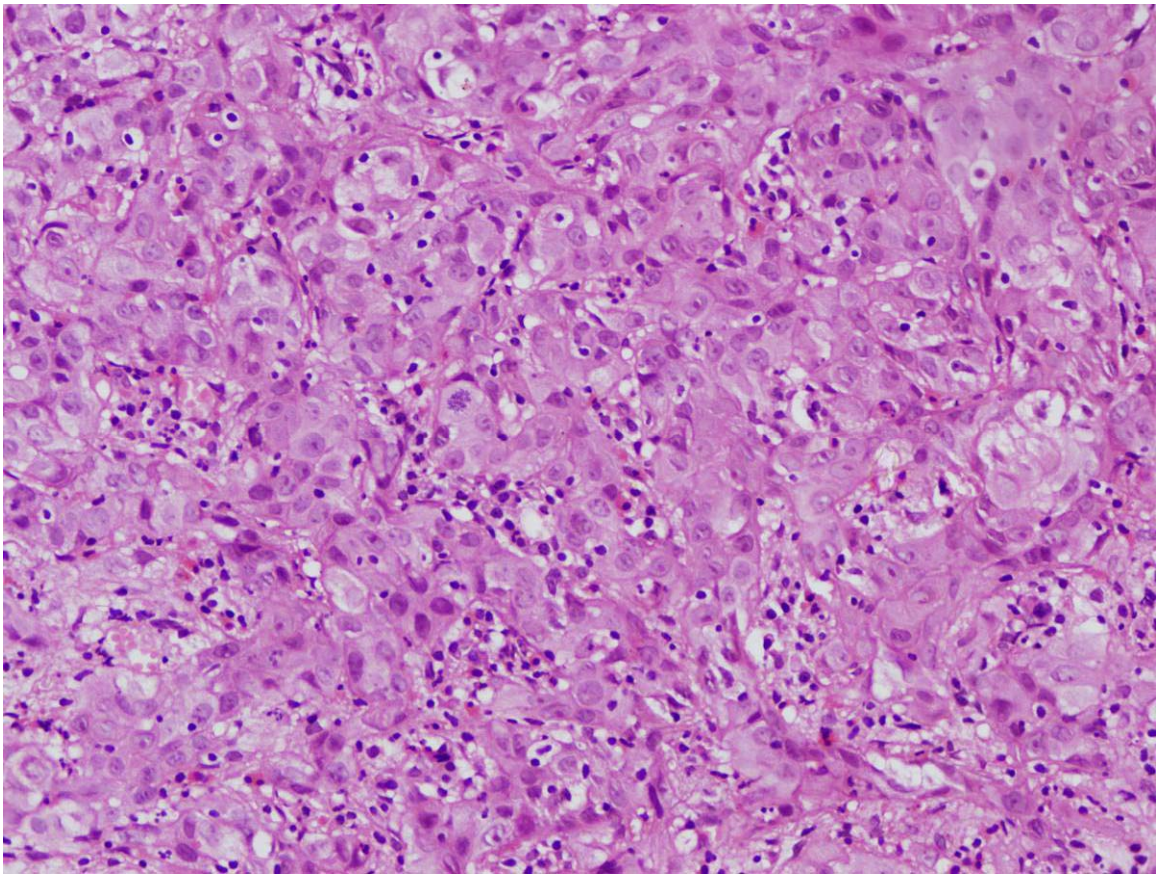


Figure (18): Squamous cell carcinoma, poorly differentiated (H&E. X40).

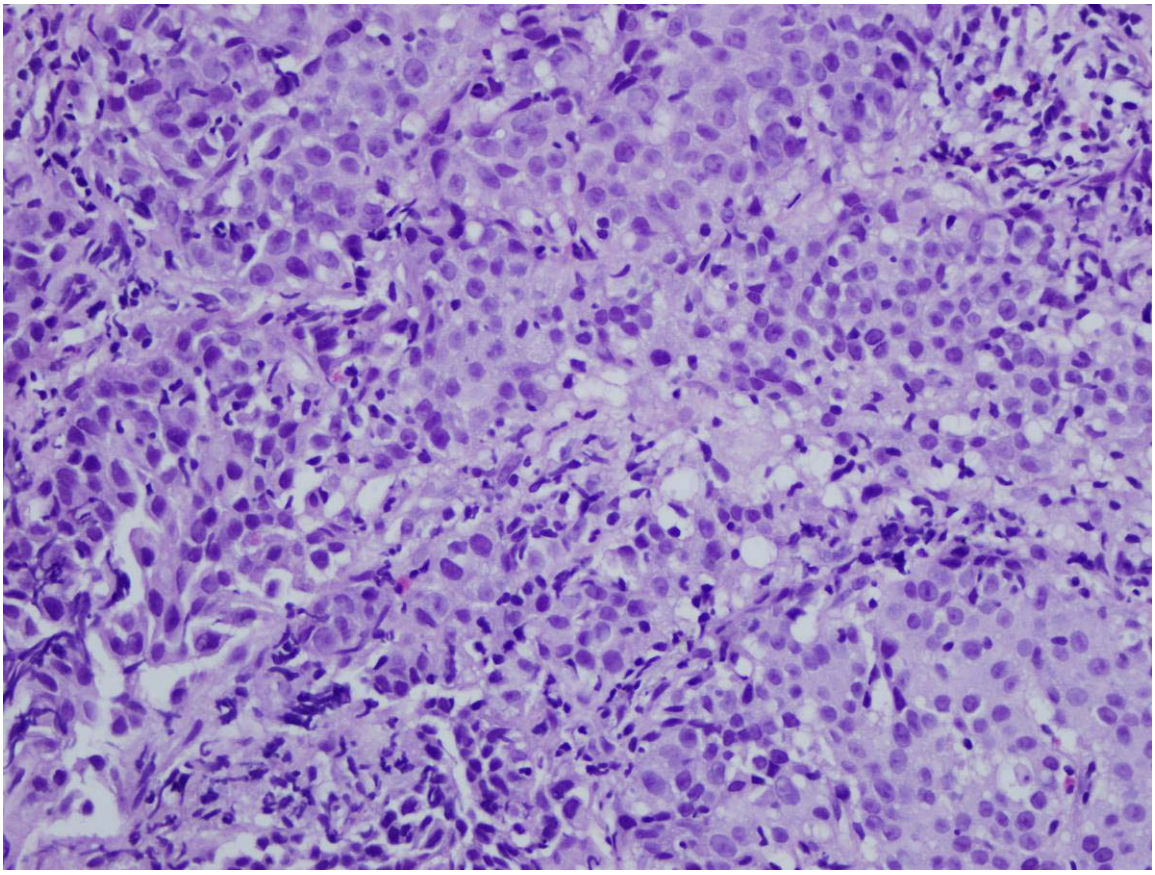


Figure (19): Infiltrative urothelial carcinoma, with squamous differentiation (H&E. X40).

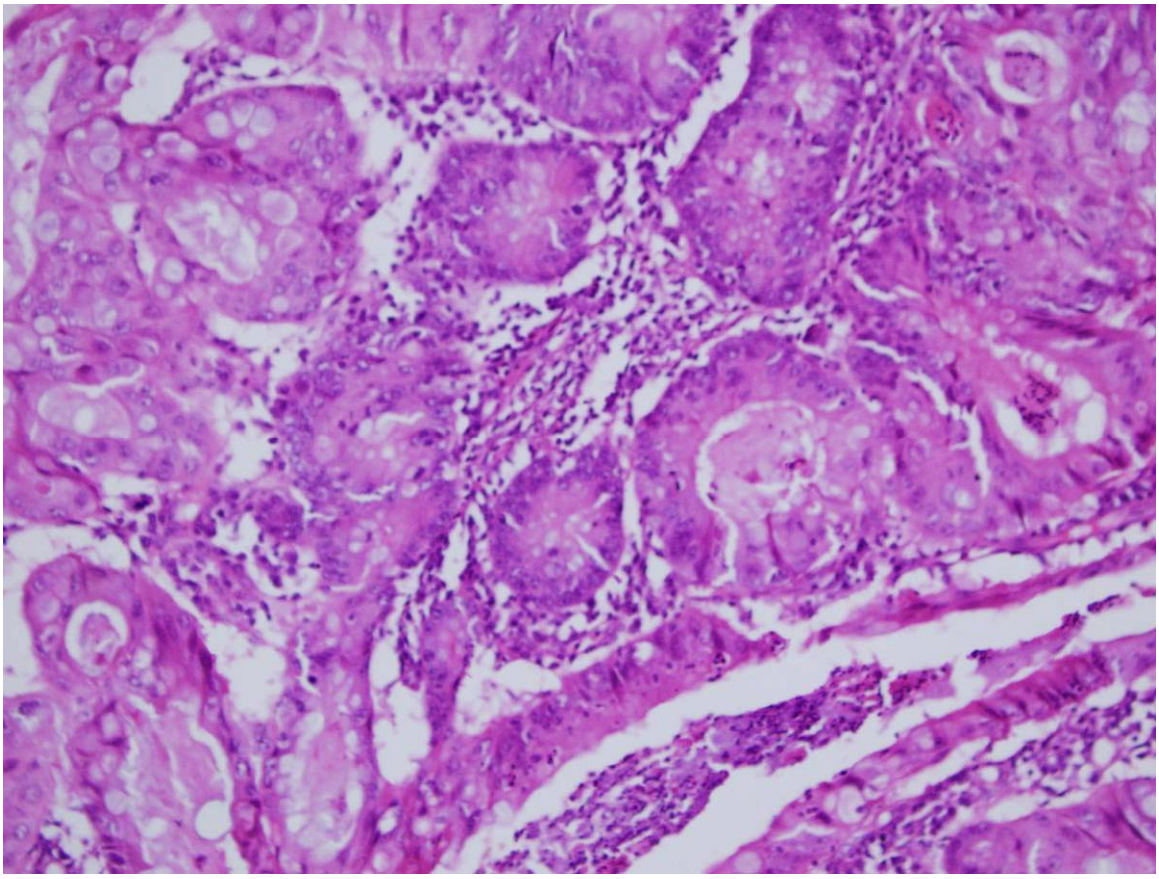


Figure (20): Adenocarcinoma of the urinary bladder. Multiple glands embedded in a loose stroma (H&E. X20).

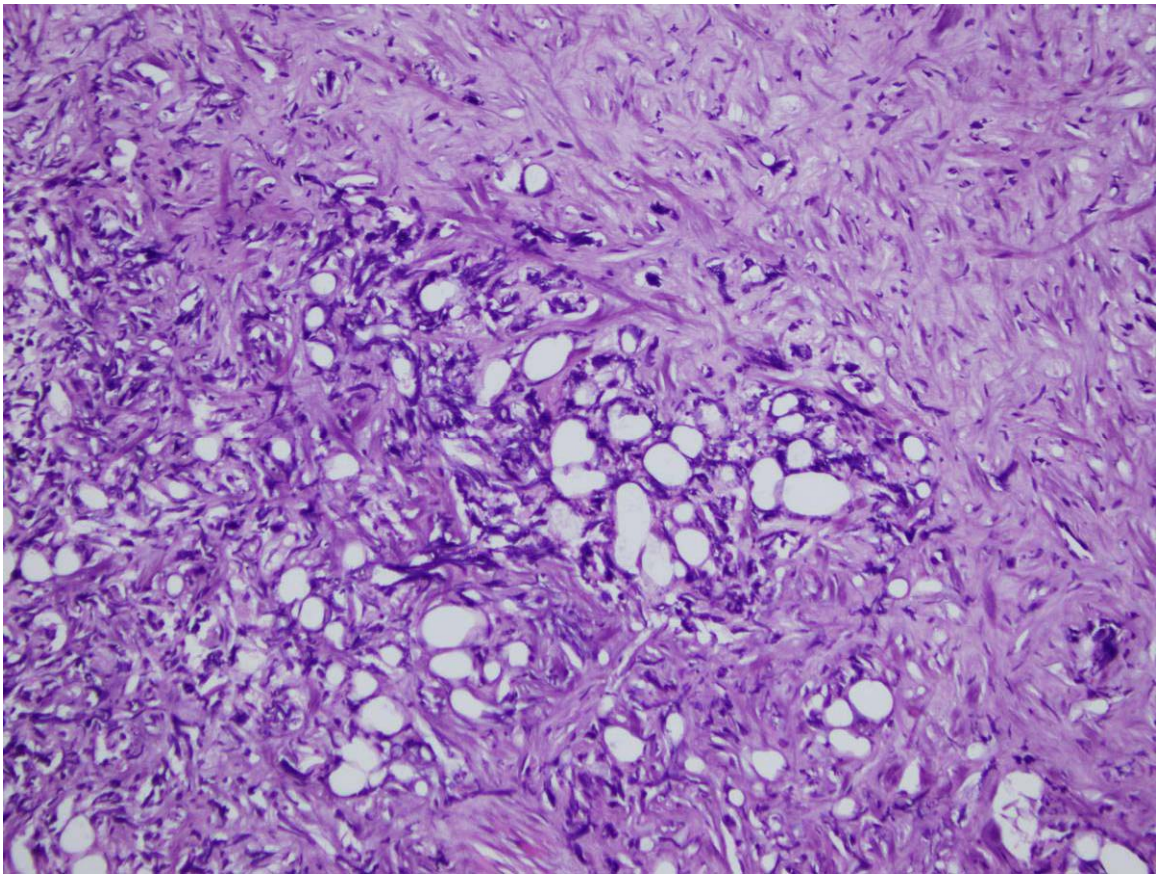


Figure (21): Urinary bladder liposarcoma (H&E.X20)

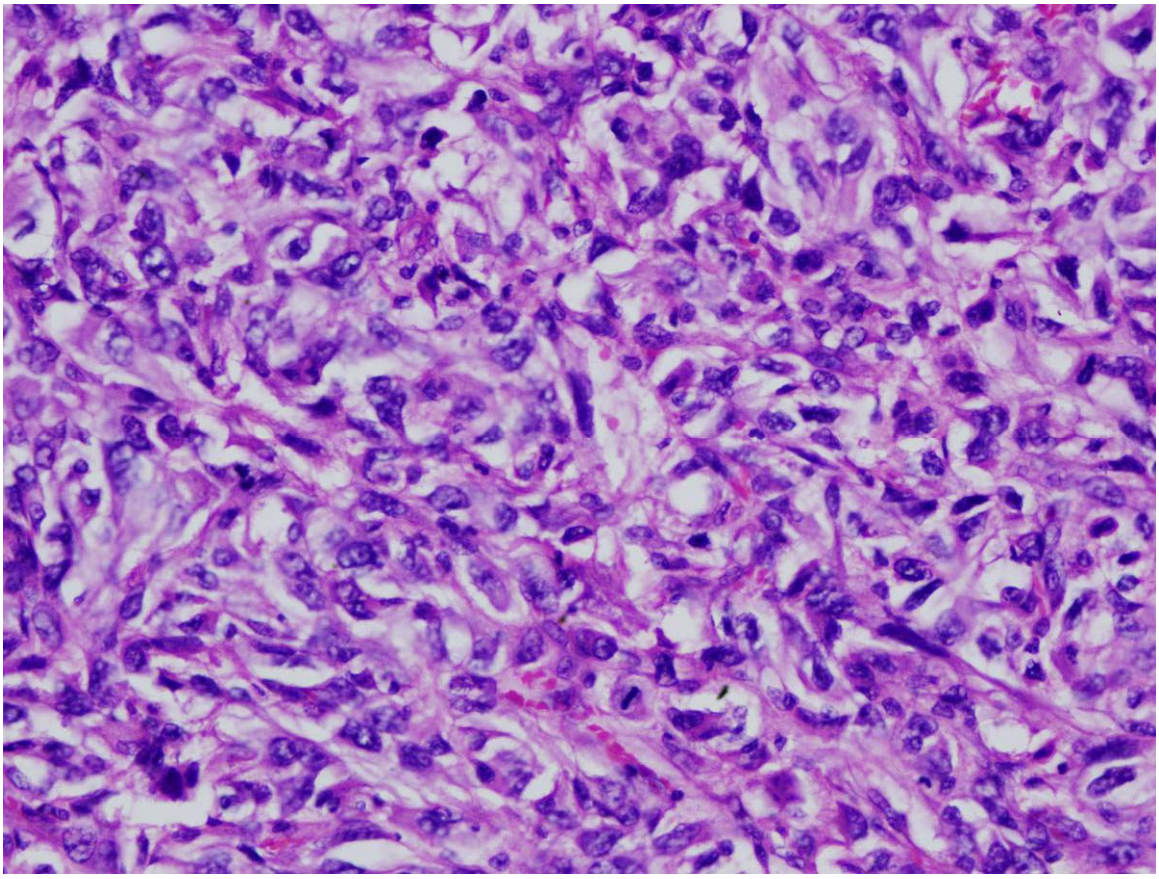


Figure (22): Urinary bladder malignant fibrous histocytoma (H&E. X40)

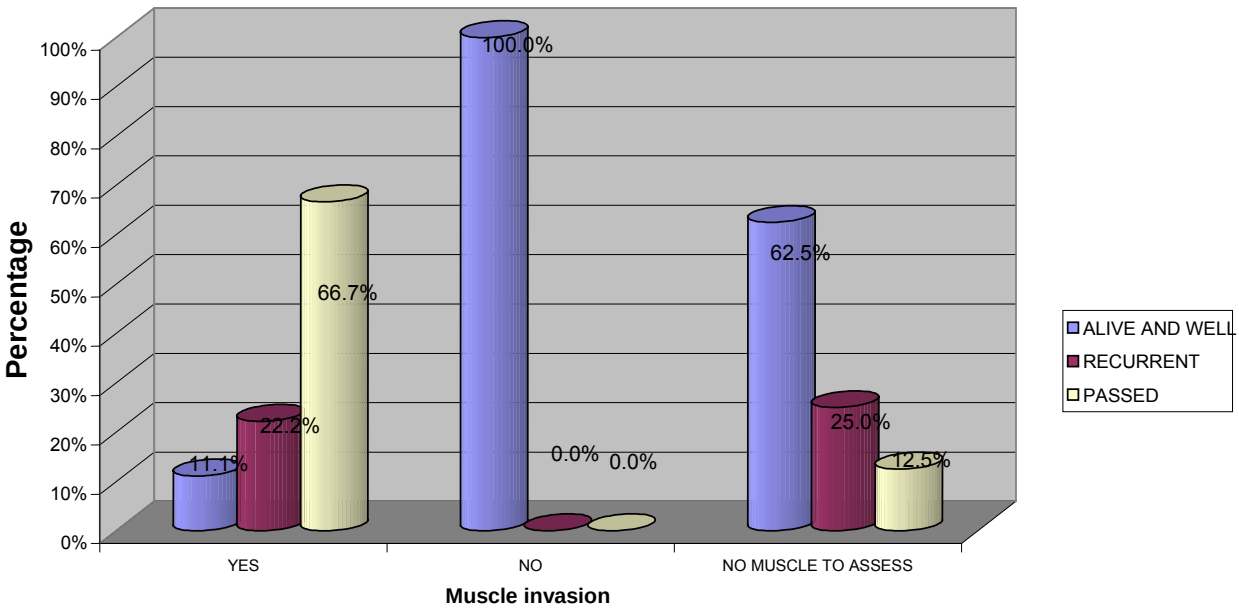


Figure (23): Relationship between muscle invasion and outcome of UBN in the studied patients (P=0.002)

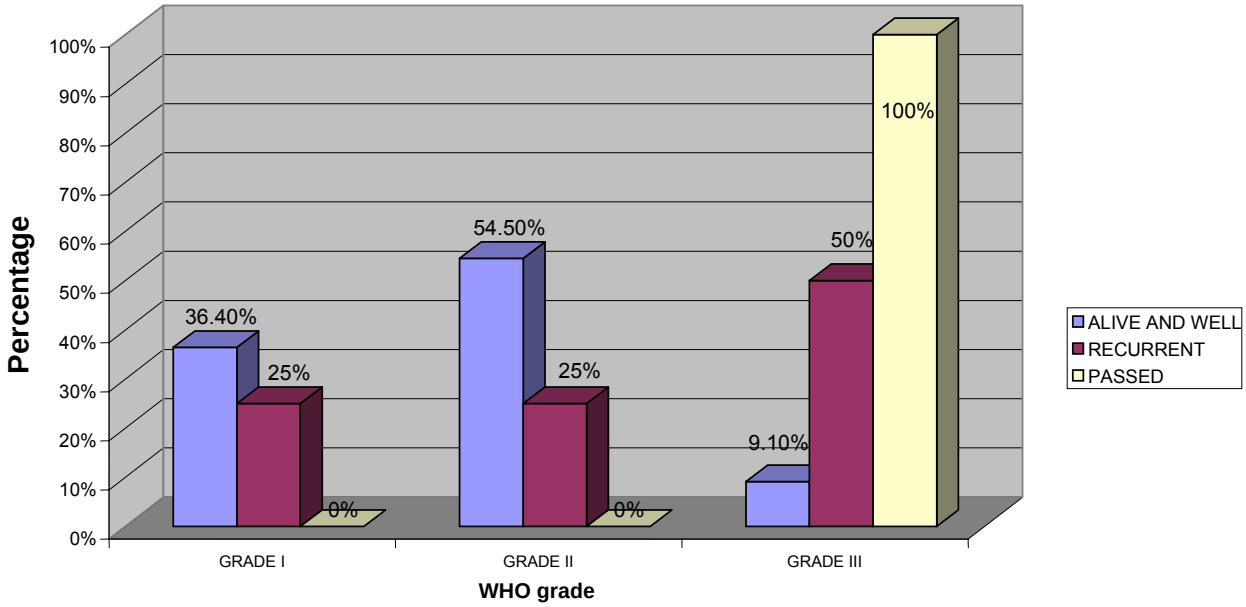


Figure (24): Relationship between grades and outcome of UBN among the studied patients (P=0.006)

Table (1): Sex distribution and male to female incidence rate ratios for TCC and SQCC among the studies patients

	Male		Female		Incidence Rate Ratio
	Frequency	Percent	Frequency	Percent	
TCC	62	86.1%	10	13.9%	6.2:1
SQCC	18	69.2%	8	30.8%	2.3:1

Table (2): Distribution of risk factors of UBN in the studied patients

Risk factor	Yes	Valid percent	No	Valid percent	Valid No
Tobacco smoking	18	43.9%	23	56.1%	41
Industrial occupation	0	0.0%	36	100%	36
Use of analgesics	0	0.0%	36	100%	36
Use of medical drugs	0	0.0%	36	100%	36
History of urinary schistosomiasis	16	38.1%	26	61.9%	42

Table (3): Presenting symptoms of UBN among the studied patients

Symptoms	Frequency	Percent
Gross haematuria	75	84.3%
Microscopic haematuria	3	3.4%
Painful micturition	35	39.3%
Urgency and frequency	14	15.7%
Palpable pelvic mass	3	3.4%
Others	41	46.1%

Table (4): Localization of UBN in the studied patients

Site	Frequency	Percent
Lateral walls	36	45%
Anterior wall	5	6.3%
Posterior wall	4	5.0%
Dome	3	3.8%
Neck	2	2.5%
Ureteric orifices	2	2.5%
Multiple	28	35.0%
Total	80	100%

Table (5): Type of specimens of the studied patients

Type of specimen	Frequency	Percent
TUBP	82	77.4%
TURBT	18	17.0%
Cystectomy	4	3.8%
True-cut needle biopsy	1	0.9%
Laprotomy	1	0.9%
Total	106	100%

Table (6): WHO grading of TCC cases in the studied patients

Tumour grade	Frequency	Percent
Papilloma	2	2.6%
Grade I	17	22.4%
Grade II	24	31.6%
Grade III	33	43.4%
Total	76	100%

Table (7): WHO/ISUP grading of TCC cases in the studied patients

Tumour grade	Frequency	Percent
Papilloma	1	1.3%
Neoplasm of low malignant potential	1	1.3%
Low grade papillary carcinoma	40	52.6%
High grade papillary carcinoma	33	43.4%
Flat	1	1.3%
Total	76	100%

Table (8): Distribution of treatment used in the studied patients

Treatment	Frequency	Percent
TURBT	27	25.5%
TURBT+ Radiotherapy	10	9.4%
TURBT+ BCG	6	5.7%
Radiotherapy	6	5.7%
Salvage cystectomy+ diversion of urine	3	2.7%
Salvage cystectomy	2	1.9%
Bypass+ Radiotherapy	1	0.9%
S. cystectomy+ Radio	1	0.9%
Debulking+ cystodithermy	1	0.9%
Radical cystectomy	1	0.9%
Urine diversion	1	0.9%
None	2	1.9%
Total	106	100%

Table (9): Outcome of UBN in the studied patients

Outcome	Frequency	Percent
Passed	15	46.9%
Alive and well	12	37.5%
Alive with recurrences	4	12.5%
Alive and ill	1	3.1%
Total	32	100%

4-1- DISCUSSION

This is a descriptive retrospective study about UBN in Sudanese patients. It was carried out in the period from January 2004 to December 2005 and includes analysis of 106 cases. It was conducted in two main urological centres as well as the National Health Laboratory.

Urinary bladder neoplasms are a heterogeneous group of tumours with different subtypes and different behavioural processes. This had led various authors to study different and specific entities within the same topic, the thing that makes comparison difficult. Few similar epidemiological and clinicopathological studies were done. Instead there is a lot of work in the diagnostic markers, especially cytogenetically, worldwide. In Sudan, one remote similar study was conducted in the period of January 1984 to December 1988.[30]

The last available data shows that bladder cancer represents 4.3% of all cancer cases registered at the Cancer Research Centre, NHL (The seventh common malignancy in men in Sudan).[101] An epidemiological search on UBN revealed a relatively low incidence of UBN in Sudan, compared to developed countries.

Using the Age Standardized Rate (ASR) which is expressed per 100.000 populations, it is 4.7 in Sudan, while 24.5 in USA and 17.0 in UK.[1] It is also lower than incidence in Egypt (37.1) and Iraq (17.7), both countries are known for their high prevalence of urinary schistosomiasis. ASR in Sudan is higher than it is in Kenya.[1]

In this study, bladder cancer accounts for 0.9% of the total number of cancer cases registered during the period of the study. It is not the exact incidence because many other cases were diagnosed in special laboratories, other hospitals, or clinics and were not registered. The real number of UBN is far greater than that registered in the NHL. In Sudan as in most developing countries, there is at present no reliable statistical information on absolute cancer rates.

According to the available data during the later years in Sudan, there has been a significant increase not only in the total number of cancers but also in the cancers of urinary bladder. Salwa Sir El khatim reported one hundred and ninety six patients seen at four urological centres as well as the Radiation and Isotope Centre, Khartoum, in the period January 1984 to December 1988, while this study reported 141 cases reviewed in three centres in two years interval. The socioeconomic changes

and urbanization, which had taken place in Sudanese society, entails characterization of this cancer, which is usually linked with economic development.

In this series, the commonest age group (60- <80) is similar to that reported by Waihenya CG and Mungai PN, but different in Salwa's study , where it was 50 – 70 years.[29,30] The median age of patients was 61 years which is higher than that of Zulfo's studied patients (51.1 years).[102] The mean age of this study is 59.5 years which is close to that reported from United States (57.8 years) but lower than that reported from Greece (66.7 years).[103, 65]

In this study, our results are in accordance with the literature regarding the occurrence of high number of cases among males. The male to female ratio (4.6:1) is similar to Salwa's study and also to a study carried in Kenyatta National Hospital, Nairobi, Kenya (4:1) and Saudi Arabia (4.4:1).[30,29,26] It differs from that done by Nazar Zulfo about superficial transitional bladder cancer where the male to female ratio was 1:1.[102] It is higher than ratios reported from United States (2.4:1) and Greece (3.9: 1).[103, 65]

Geographically, most of the patients (37.1 %) were originally from the North region of Sudan. Central Sudan achieved the third percent (24.3%).This is not similar to Salwa's study where most of

her patients were originally from central region which is the area most heavily affected with schistosomiasis in Sudan.

The explanation to the lower incidence of UBN in the central region in our study inspite of the high infestation rate with urinary schistosomiasis could lie either in the fact that people in endemic areas receive anti-bilharzial treatment frequently at an earlier age or that many patients with squamous cell carcinoma in the bladder die before having any medical advice. A third possibility is that urinary schistosomiasis run a more benign course and its natural history become different.[104]

The West region of Sudan showed the 2nd high incidence (35.7%), while no one was found to be from the South. These discrepancies may not be due to real geographical variation but rather to the surgical, histopathological, and treatment services available in the Capital. Poor financial status, difficult transportation, war situations, and lack of awareness may be among the major reasons why patients do not report from Southern and Eastern Sudan.

Tribes of the North dominated, as most of the studied patients were from the North region. Galeen tribe showed the highest incidence. This is probably due to their easy transportation to Khartoum.

In this study, most of the patients were labourer (44.4%). 41.7% of them were farmers. These results were similar to those reported from Kenya and Egypt.[29, 105] It has been suggested that this could be attributed to the fact that squamous cell carcinoma of the bladder which is common in areas endemic with urinary schistosomiasis occurs mostly in farmers by the virtue of being subjected more to infestation by schistosomiasis. In Egypt it is well known that this sector of the community is the main victims of schistosomiasis and its complications including cancer. This makes the male to female ratios higher in areas endemic with schistomiasis such as Egypt (9:1) compared with non-schistomsomal countries such as United States (2.4:1) and Greece (3.9:1).[103, 65]

In the present series, the interpretation of risk factors of UBN was a bit strange. Although tobacco smoking is a well established risk factor of UBN in the literature, this study showed no significant relationship between tobacco smoking and development of UBN among the studied Sudanese patients (P= 0.275). This could be explained by the low number of patients that were interviewed directly for tobacco smoking in the study 41 (38.7%) and some of them may omit the truth or did not mention that they smoke once upon their lives even they were not smokers during the study

period. Limited background history and poor clerking in the patient's files might also be implicated.

In the current study, there was no single case that showed a positive history of either occupational exposure or chronic use of analgesics containing phenacetin or medicinal drugs. Sudan is not an industrial country, this might lie behind the finding that occupational exposure is not considered to be a risk of UBN among Sudanese patients. They also use paracatamol and aspirin as analgesics, and do not use phenacetin compounds.

Patients who use medicinal drugs such as cyclophosphamide in Sudan usually die because of original disease rather than developing UBN.

Arsenic-contaminated water was not studied as a risk factor of UBN among Sudanese patients in this study because it needs a biochemical analysis of water. It is suggested to be behind the high incidence of UBN in areas not endemic with schistosomiasis. Arsenic is used in pesticides and North Sudan which is an agricultural area showed a high incidence of UBN in the present study. It remains to be studied.

In the present series 38.1% of patients gave a past history of urinary schistosomiasis. 84.6% of the patients with SQCC had a past history of urinary schistosomiasis. This study yielded a highly

significant relationship between urinary schistosomiasis and development of SQCC (P=0.0001).

In Salwa's study 31% of patients gave a past history of urinary schistosomiasis, while in Iraq 50% had a positive history of urinary schistosomiasis.[30, 106]

The commonest presenting symptom was haematuria occurring in 87.7% of our patients. This was described as gross and painless haematuria in 84.3% of cases. Haematuria is by far the commonest and can be the only presentation of urinary schistosomiasis. Patients who develop bladder neoplasm on top of schistosomaisis do not appreciate development of newer symptoms and they attribute haematuria to schistosomiasis and accordingly most of them present with advanced disease. This in part explains the large number of patients presenting with other symptoms (46.1 %) including suprapupic mass, obstructive uropathy and weight loss on the first visit.

These results were similar to those of Salwa Sir El khatim (82% of patients presented with total painless haematuria) as well as Zulpho (84.6% of patients presented with haematuria).[30, 102]

The exact time lapse between the beginning of the symptoms and the diagnosis of UBN is variable. In this study, it varies from one week to six years.

In this study, the percentage of cases of UBN diagnosed first by ultrasonography was high (75.7%), compared to 21.4% by cystoscopy and biopsy. Ultrasonography is a non-invasive radiological procedure which is easy and available, this is why it is requested first. It gives the suggestion of UBN, but the definite diagnosis is by cystoscpy and biopsy.

IVU, which needs dye contrast, although useful its role in diagnosing UBN is declining. It diagnosed only 2.9% of patients in this study. None of the patients in the study was diagnosed by CTscan, MRI or urinary cytology. CT scan and MRI are costy procedures and not yet commonly available in Sudan. They were requested later in the disease and are useful primarily for evaluating the upper urinary track and in staging the more advanced lesion.

Urine cytology is of little practical value in the initial evaluation of most bladder tumours because of their accessibility to formal biopsy. The greatest value of urinary bladder cytology is in the follow up evaluation of patients who have received surgical or radiotheraputic treatment for bladder neoplasm.

Cystoscopically, the lateral walls were found to be the commonest site of occurrence of UBN in our series (45%). This is nearly similar to what was reported from UK where the lateral walls

were affected in 37% of cases.[I6] It differs from Salwa's study where the bladder base was found to be the commonest site of occurrence of cancer (28%).[8] It also differs from what was reported from Egypt where the base was affected in 44.6% of cases.[107]

Although most of our cases presented with large tumour size (>6 cm) (58.5%), tumour size did not show significant relationship to outcome (P=0.761).

Since cystoscopy and biopsy is the mainstay of diagnosis, most of the specimens in this study were transurethral bladder biopsies (77.4%).

The feature that the disease in our patients have in common with non-bilharzial bladder neoplasms is that histologically the majority (67.9%) were transitional cell carcinomas, while sqamous cell carcinoma accounts for 24.5% of the cases which is high compared to a frequency of less than 5% in UK and USA.[23] Yet, very low compared to the figures from Egypt where sqamous cell carcinoma forms the bulk of cases (66.7%), and transitional cell carcinoma forms only 23.4%, and from Iraq where sqamous cell carcinoma forms 65% and transitional cell carcinoma forms only 28% of cases.[107,106]

Surprisingly, in USA - a non-bilharzial country- there are differences in histology by race, with Whites having 95% urothelial

and 1.3% SQCC, while the proportions are 87.8% and 3.2%, respectively, in Blacks.[23] In South Africa, there are marked differences in histology between Blacks (36% SQCC, 41% urothelial) and Whites (2% SQCC, 94% urothelial).[23] The association between race and the prevalence of SQCC remains to be answered.

The evidence by the authors already cited in favour of an association between urinary shistosomaisis and bladder neoplasm has been advanced on epidemiological, clinical and morphological grounds.[23] They point to the finding that bladder neoplasm is much more frequent in areas where shistosomaisis is prevalent than in regions where it is not known or is of minor importance. However, challenging the arguments to the contrary has been produced by other workers. For instance, it is mentioned that vesical cancer is not as common in some African countries despite shistosomal endemicity. Furthermore, in Uganda, squamous cell carcinoma is the commonest histological type of bladder cancer in the presence of little or no shistosomal infection. Doge (1962) found only one case of vesical shistosomaisis in 81 bladder cancers and Anthony (1967) found none in 127 cases. These arguments have focused attention on other operating factors. In Uganda for example, it has been suggested that urinary obstruction consequent on urethral

stricture from gonococcal infection might be incriminated.[108] As regards to the statistical relationship of bladder cancer to shistosomal endemicity, it has been argued that the host-parasite relationship might differ from one place to another, that various strains might differ in their genetic experience and susceptibility, and that not merely the presence but also the severity of infestation has to be taken into consideration.[109-111]

Different variants of TCC were identified in this study including the nested variant which is rare and a low grade TCC with lymphoplasmacytic infiltrate in the fibrovascular core which is unique (not found in the literature).

In our patients, 51.3% of the TCC neoplasms were of papillary configuration, 25% were solid, and 23.7% were both papillary and solid. This is in contrary to the findings of Salwa Sir El Khatim where 58% of tumours were solid, and only 33% were papillary. It is also not in agreement with reports from Egypt and Iraq where solid fungating tumours constitute 68.5% and 52% of all bladder neoplasms respectively. It should be noted that the solid tumours form only 18.9% of non-bilharzial bladder cancer, 81.1% of them being papillary.[112]

The classification and grading of non-invasive, intraepithelial neoplasms of the urothelium are based on the morphological

pattern of growth- that is, papillary or flat- and on their degree of architectural and cytological abnormalities. Recent advances in the morphological, molecular, and quantitative evaluation of these lesions have contributed to the refinement of the current classification and grading schemes. However, some controversies on the precise criteria and terminology, especially when the papillary lesions are concerned, are still present.[113]

Changes in classification have their own inherent problems, tending to lead to confusion, at least for a period of time. From practical point of view, in this study we used both the WHO and the latest WHO/ISUP classification.

The key points of the latest WHO/ISUP classification of non-invasive urothelial tumours are: the description of the categories has been expanded in the current version to improve their recognition; one group (papillary urothelial neoplasm of low malignant potential) with particularly good prognosis does not carry the label of "cancer"; it avoids use of ambiguous grading such as grade 1/2 or 2/3 (according to the WHO classification published in 1973); the group of non-invasive high grade carcinomas large enough to contain virtually all those tumours that have biological properties (and a high genetic instability) similar to those seen in

invasive urothelial carcinoma. This scheme is meant to replace the 1973 WHO classification.[114]

Samaratunga et al investigated the risk of progression for the WHO/ISUP 1998 and WHO 1973 classifications. They observed progression in 8% of patients with PUNLMP and 11% of patients with grade I papillary carcinoma (WHO classification). The same group claim an advantage of the WHO/ISUP system over the WHO system in that the WHO/ISUP classification recognised a larger proportion of cancers with a poor prognosis.[115]

Nevertheless Oosterhuis et al found that the prognostic value of the WHO/ISUP classification is limited, thus questioning the clinical role of this new system in comparison with conventional grading systems .[116]

According to Bostwick and Mikuz, the WHO 1973 classification and grading of bladder tumours is recommended with minor modifications for international use to allow valid comparison of results between different clinical centers.[117]

Seitz M, et al presented the new 2004 WHO/ISUP classification of urinary bladder tumours emphasizing the changes in relation to the former classifications focusing on histological typing, grading and molecular characterization. They recommended that until the new classification is finally validated and those working in the field

have become familiar with it, the WHO classification of 1973 should be mentioned additionally in the histopathology report.[118]

In our study we found closely similar findings of both classification schemes concerning grade III (WHO classification) and papillary urothelial neoplasms, high grade (WHO/ISUP classification) with a percentage of 44 and 43.4 respectively. The explanation of this high percent of high grade tumours at diagnosis might be the late presentation of our patients.

The high percent of papillary urothelial neoplasms, low grade in this study was attributed to that we considered both grade I and grade II (WHO classification) as papillary urothelial neoplasms, low grade in the WHO/ISUP classification to avoid ambiguous grading. This was a pitfall, because the term "PUNLMP" was introduced to replace WHO grade I carcinoma in recognition of the low probability of recurrence or progression of this neoplasm, especially after complete removal, and the preference not to label these patients with the term "cancer".

In the current study, concerning the histological type SQCC, most of the cases were poorly differentiated (42.9%) and none keratinized (67, 9%). This could be explained partially by the late presentation of our patients and to some extent by the aggressive nature of the SQCC.

Twenty five percent of our patients who had non-invasive tumours at presentation were treated by TURBT alone. In 9.4 % of the resected specimens at histology showed invasion of the superficial muscles and those had supplementary radiotherapy. The percent of patients who had TURBT + BCG or received radiotherapy alone (each 5.7%) exceeds that of patients underwent salvage cystectomy and diversion of urine (2.7%).

The aim of urinary bladder cancer treatment with intravesical chemotherapy is three fold: to eradicate existing diseases, prevent recurrence and prevent tumour progression.[119] Comparing resection with and without adjuvant intravesical chemotherapy, an approximately 15 % short – term decrease in tumour recurrences with chemotherapy is obtained, although no effect on progression was proven.[120]

The importance of early administration has been highlighted by the positive results of a single, early instillation of chemotherapy, with a reported mean reduction in recurrence rate of 12-27%. Immunotherapy in the form of bacillus Chalmette-Guerin has generally proven more efficious than chemotherapy.[120]

T1 transitional cell neoplasm of the urinary bladder is associated with a significant risk of tumour progression when

transurethral resection (TURBT) is the only treatment. Additional intravesical immunotherapy can reduce this risk; however, long-term results of more than 5 years of follow up indicate that almost half of the patients may loose their bladder or even die due to recurrent tumour.

The alternative to TURBT is cystectomy at either the initial presentation or time of first recurrence. However, although the results of this treatment strategy are encouraging, an unknown percentage of patients will loose their bladder and go on to experience all possible complications of urinary diversion unnecessarily. The central issue of conservative treatment but also the indication for cystectomy is the quality of TURBT.[121] Moreover, even in cases of a so-called 'correct TURBT', a significant percentage of residual tumour is left behind and will be the source of local recurrence or progression.[121]

Janson S, et al studied residual tumours at a second-look resection in patients resected 4-8 weeks earlier for T1 tumours of the urinary bladder. They concluded that the majority of residual tumours detected at this stage are potentially dangerous; therefore, early second-look resection followed by intravesical installation therapy is mandatory in patients with T1 tumours of the urinary bladder.[122]

In this study, only thirty two patients were followed during the two years of the study. Of them, 46.9% passed. The commonest cause of death in our patients was renal failure due to involvement of the ureters rather than wide-spread metastasis.

Inspite of the short duration of the study, follow up was a real problem. This is related to many factors, the most important of which is that most patients came from rural areas where means of transportation and communication to the urological centres in Khartoum are difficult and costy, especially in the raining season when this can be impossible. The second reason is that very few rural hospitals are equipped with cystoscopic armamentarium and nearly all the few urological surgeons are based in Khartoum. A third reason which made follow up difficult in those patients is that our patients do not appreciate coming for routine follow up or check-cystoscopy once they are symptom-free especially , haematuria-free .

The recurrence rate within five years after partial resection was reported as high as 78%.[123] However, in our series only 12.5% of resected group show recurrences and this low percentage is mostly attributed to the difficulties in follow up of patients.

This study proved a statistically significant relationship between muscle invasion in TCC and the outcome of the disease (P=0.002). This is similar to the results of Blaveri E, et al who evaluated the associations between measures of genomic instability and bladder cancer clinical phenotype using array-based comparative genomic hybridization. They found that the fraction of genome altered (FGA) was associated with worse outcome in muscle-invasive tumours, independent of other clinicopathologic parameters (P=0.002).[124]

In this study, tumour grade showed a significant association with the outcome (P=0.006). This is closely related to the findings of Messing EM, et al, that of the high-grade or invasive cases, the proportion of late stage (T2 or higher) tumours was significantly lower in the screening-detected bladder cancers compared to unscreened ones (P-0.007). They drew attention to the importance of haematuria home screening which detects high-grade cancers before they become muscle invading and significantly reduces bladder cancer mortality.[125] However, testing for microhaematuria does not meet the requirements of a modern screening and diagnostic test. Better alternatives are presently available, and in the near future we will likely see urine tests for specific clinical conditions.[126] Current studies do not support the routine screening

for bladder cancer. However, prospective long-term studies are required to evaluate the benefits of bladder cancer screening, particularly in those at high risk.[127] It is time to detect high-grade cancers early, in a high risk population, cytogenetically in order to reduce bladder cancer mortality.

4-2- CONCLUSION

When all the findings in our series are considered together, it can be said that pattern of urinary bladder neoplasms in Sudan tend to share some common features with bilharzial bladder cancer in other countries on one hand, and with non-bilharzial bladder neoplasms on the other.

Possibly more cases of bladder neoplasms are emerging in the recent years either because the level of awareness among the patients is increasing or the methods of early detection of tumours are improving as improvements in cysoscopies and other investigation tools.

Despite limitation in the background history, detailed histological diagnosis and staging, this study showed a significant relationship between urinary schistosomal infestation and development of squamous cell carcinoma of the urinary bladder.

A significant correlation was identified in this study between tumour grade as well as muscle invasion and the outcome of urinary bladder neoplasms.

4-3- RECOMMENDATIONS

A more accurate assessment awaits detailed prospective studies comparing regions within Sudan itself where schistosomiasis is endemic with others where it is not known to occur.

More searches are needed to be carried to address the possible environmental and community related risk factors such as arsenic and others, especially in Northern and Western Sudan.

We feel that a close follow up of patients with chronic urinary schistosomiasis by regular cystoscopies, possibly cytology and histology of bladder tissue for metaplasia, urine markers, and even cytogenetically can be of some help for early detection of this aggressive neoplasm.

The community medicine and public health services has a big role to play in teaching people in the endemic areas, and measures should be taken to detect complications at an early stage and this can be achieved only at a primary medical care level.

Detailed histopathological diagnosis, grading and staging, and improvement of cancer reporting and registering are highly recommended.

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بسم الله الرحمن الرحيم

University of Khartoum
Faculty of Medicine
Postgraduate Medical Studies Board
Questionnaire

Bladder Cancer

Date: / / Serial No.: ☐

Hospital: 1-Ibn Sina ☐ 2-Suba ☐ 3-NHL (Khartoum) ☐

- Lab. No.: ……. Consultant in charge: …….

File No. ……

1- Name: …….. Address: …….

2- Age (in years): …….

3- Gender: a- Male ☐ b- Female ☐

4- Tribe: ……5-Occupation: …….

6- Residence: ……7-Origin: ……

8- Risk factors: History of:

a- Tobacco smoking. Yes ☐ No ☐ Not known: ☐ ☐

b- Industrial occupation. Yes ☐ No ☐ Not known: ☐

c- Analgesics. Yes ☐ No ☐ Not known:

d- Medicinal drugs. Yes ☐ No ☐ Not known: ☐

e- U. Schistosomiasis. Yes ☐ No ☐ Not known: ☐

9- Clinical remarks:

a- Haematuria : i- Gross . ☐
ii- Microscopic . ☐

b- Painful micturition. ☐

c- Urgency and frequency. ☐

d- Palpable pelvic mass. ☐

e- Others:…….

10- Diagnosed by:

a- Cystoscopy and biopsy . ☐

b- Imaging : i- IVU ☐ ii- U/S ☐
iii- CTscan ☐ iv- MRI ☐

c- Surgical resection. ☐

d- Urine cytology. ☐

11- Cystoscopy findings: …….....

9- Histopathology:

Type of specimen: TUBP ☐ TURBT ☐ Cystectomy ☐

Gross: ……..

Microscopy:…….

Diagnosis:……

Grading:……...